STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 134341

TO: Cybille Delacroix **Location: rem/3a78/3c70** **Art Unit: 1614** **Tuesday, October 05, 2004** **Case Serial Number: 10/790943**	**From: Peggy Ruppel** **Location: Biotech-Chem Library** **REMSEN 1B65** **Phone: 571-272-2557** **Peggy.Ruppel@uspto.gov**

Search Notes

The results of your search request are attached. I've flagged the inventors' work in the citations and the assignee searches.

Please contact me if you have any questions or comments about the search strategy or the results.

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Access DB# 134341

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: C. Delacroix-M Examiner #: 71100 Date: 10-5-04
Art Unit: 1614 Phone Number: 272-0572 Serial Number: 10/790,943
Mail Box and Bldg/Room Location: 43C70 43A78 Results Format Preferred (circle): PAPER DISK E-MAIL
If more than one search is submitted, please prioritize searches in order of need. ME

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention:

Inventors (please provide full names): Please see attached

Earliest Priority Filing Date:

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

RECEIVED OCT -5 2004

Please search a method of treating cancer by administering a composition having:

(1) OMXAA → 5,6 dimethylxanthenone (structure is attached)

AND

(2) a known anticancer compound such as platinum compounds (carboplatin, cisplatin), gemcitabine, etoposide, vincristine, 5-fluorouracil, cyclophosphamide, irinotecan, doxorubicin.

Claims are attached w/ key terms highlighted. Thanks

STAFF USE ONLY

Searcher:
Searcher Phone #:
Searcher Location:
Date Searcher Picked Up:
Date Completed:
Searcher Prep & Review Time:
Clerical Prep Time:
Online Time:

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

STN
Dialog
Questel/Orbit
Dr. Link
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (8-01)

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspat01plr

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'HOME' AT 15:01:48 ON 05 OCT 2004
FILE 'HOME' ENTERED AT 15:01:48 ON 05 OCT 2004

=> b reg
FILE 'REGISTRY' ENTERED AT 15:01:52 ON 05 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8
DICTIONARY FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l6
L6 1 SEA FILE=REGISTRY ABB=ON PLU=ON DMXAA/CN

=> d ide l6

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 117570-53-3 REGISTRY
CN 9H-Xanthene-4-acetic acid, 5,6-dimethyl-9-oxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5,6-Dimethylxanthenone-4-acetic acid
CN **DMXAA**
CN NSC 640488
FS 3D CONCORD
MF C17 H14 O4
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOSIS, CA,

CANCERLIT, CAPLUS, CASREACT, CHEMINFORMRX, CIN, IMSRESEARCH, MEDLINE, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

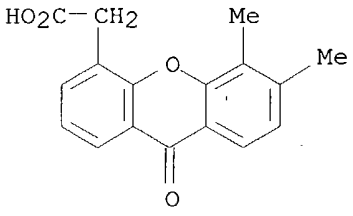
DT.CA CAplus document type: Conference; Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

121 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
121 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> b home
FILE 'HOME' ENTERED AT 15:02:08 ON 05 OCT 2004

=>

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=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 15:20:40 ON 05 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 5 Oct 2004  VOL 141 ISS 15
FILE LAST UPDATED: 4 Oct 2004  (20041004/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l18
L13         3166 SEA FILE=HCAPLUS ABB=ON  PLU=ON  WILSON W?/AU
L14          105 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SIM B?/AU
L18           19 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (SIIM B?/AU OR L14) AND L13


=> d ibib abs l18 1-19

L18  ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2004:802558  HCAPLUS
TITLE:                   Benzoazine mono-N-oxides and benzoazine 1,4 dioxides
                         and compositions therefrom for the therapeutic use in
                         cancer treatments
INVENTOR(S):             Wilson, William Robert; Pruijn, Frederik
                         Bastiaan; Siim, Bronwyn Gae; Hay, Michael
                         Patrick; Denny, William Alexander; Gamage, Swarnalatha
                         Akuratiya
PATENT ASSIGNEE(S):      Auckland Uniservices Limited, N. Z.
SOURCE:                  U.S. Pat. Appl. Publ., 88 pp.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ----------          ----   --------    -------------------    --------
     US 2004192686        A1    20040930    US 2004-766942         20040130
PRIORITY APPLN. INFO.:                      NZ 2003-524770      A  20030314
AB   The present invention relates to a synergetistic composition comprising
     one or more benzoazine-mono-N-oxides, and one or more benzoazine 1,4
     dioxides for use in cancer therapy.  The invention also provides a range
     of novel 1,2,4 benzoazine-mono-N-oxides and related analogues.  These can
     be used as potentiators of the cytotoxicity of existing anticancer drugs
     and therapies for cancer treatment.
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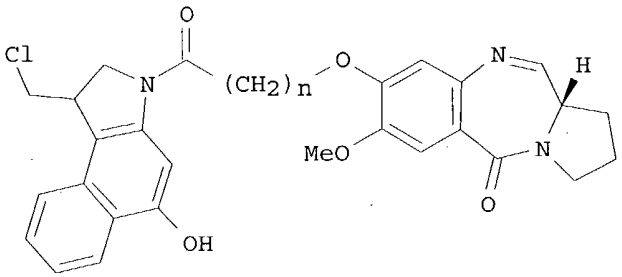
L18 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:455121 HCAPLUS
DOCUMENT NUMBER: 140:399599
TITLE: Oxygen dependence of the metabolic activation and cytotoxicity of tirapazamine: Implications for extravascular transport and activity in tumors
AUTHOR(S): Hicks, Kevin O.; **Siim, Bronwyn G.**; Pruijn, Frederik B.; **Wilson, William R.**
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.
SOURCE: Radiation Research (2004), 161(6), 656-666
CODEN: RAREAE; ISSN: 0033-7587
PUBLISHER: Radiation Research Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypoxic cytotoxin tirapazamine (TPZ) is currently in phase III clin. trial and appears to have clin. activity. One hypothesis as to why TPZ has been used more successfully in the clinic than most other bioreductive drugs is that its unusual O2 dependence allows killing of radioresistant cells at "intermediate" O2 concns. We have determined the O2 dependence of the metabolism of TPZ to its reduction product SR 4317, and its cytotoxicity, in stirred suspensions of HT29 colon carcinoma cells while monitoring O2 in solution with an Oxylite probe. The O2 dependence of the cytotoxicity of TPZ is entirely accounted for by its inhibition of the metabolism of TPZ, with a KO2 value (O2 concentration for 50% inhibition) of 1.21±0.09 (SEM) μM. We used this exptl. O2 dependence to extend a recent (Hicks et al., Cancer Res. 63, 5970-5977, 2003) pharmacokinetic/pharmacodynamic model for the cytotoxicity of TPZ in anoxic HT29 multicellular layers to model cell killing in tumors. The model indicates that the O2 dependence of killing by TPZ complements that of radiation well during fractionated radiotherapy. It predicts that lowering KO2 would decrease killing in radioresistant cells at intermediate O2 concns., while higher KO2 values would exacerbate metabolic consumption of TPZ and thus further impede its penetration into hypoxic regions. Raising KO2 would also increase metabolic activation at physiol. O2 concns., thereby compromising hypoxic selectivity. We conclude that the KO2 value of TPZ is indeed close to the optimum for a bioreductive drug of this class (i.e. one that kills only cells in which it is reduced).
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:64251 HCAPLUS
DOCUMENT NUMBER: 140:228751
TITLE: Selective Potentiation of the Hypoxic Cytotoxicity of Tirapazamine by Its 1-N-Oxide Metabolite SR 4317
AUTHOR(S): **Siim, Bronwyn G.**; Pruijn, Frederik B.; Sturman, Joanna R.; Hogg, Alison; Hay, Michael P.; Brown, J. Martin; **Wilson, William R.**
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.
SOURCE: Cancer Research (2004), 64(2), 736-742
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tirapazamine (TPZ), a bioreductive drug with selective toxicity for hypoxic cells in tumors, is currently in Phase III clin. trials. It has been suggested to have a dual mechanism of action, both generating DNA

radicals and oxidizing these radicals to form DNA breaks; whether the second (radical oxidation) step is rate-limiting in cells is not known. In this study we exploit the DNA radical oxidizing ability of the 1-N-oxide metabolite of TPZ, SR 4317, to address this question. SR 4317 at high, but nontoxic, concns. potentiated the hypoxic (but not aerobic) cytotoxicity of TPZ in all four of the human tumor cell lines tested (HT29, SiHa, FaDu, and A549), thus providing a 2-3-fold increase in the hypoxic cytotoxicity ratio. In potentiating TPZ, SR 4317 was 20-fold more potent than the hypoxic cell radiosensitizers misonidazole and metronidazole but was less potent than misonidazole as a radiosensitizer, suggesting that the initial DNA radicals from TPZ and radiation are different. SR 4317 had favorable pharmacokinetic properties in CD-1 nude mice; coadministration with TPZ provided a large increase in the SR 4317 plasma concns. relative to that for endogenous SR 4317 from TPZ. It also showed excellent extravascular transport properties in oxic and anoxic HT29 multicellular layers (diffusion coefficient 3 x 10-6 cm2s-1, with no metabolic consumption). Coadministration of SR 4317 (1 mmol/kg) with TPZ at a subtherapeutic dose (0.133 mmol/kg) significantly enhanced hypoxic cell killing in HT29 tumor xenografts without causing oxic cell killing, and the combination at its maximum tolerated dose was less toxic to hypoxic cells in the retina than was TPZ alone at its maximum tolerated dose. This study demonstrates that benzotriazine mono-N-oxides have potential use for improving the therapeutic utility of TPZ as a hypoxic cytotoxin in cancer treatment.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:323970 HCAPLUS
DOCUMENT NUMBER: 139:69239
TITLE: Unsymmetrical DNA Cross-Linking Agents: Combination of the CBI and PBD Pharmacophores
AUTHOR(S): Tercel, Moana; Stribbling, Stephen M.; Sheppard, Hilary; **Siim, Bronwyn G.**; Wu, Kent; Pullen, Susan M.; Botting, K. Jane; **Wilson, William R.**; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (2003), 46(11), 2132-2151
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:69239
GI



I

AB A set of chiral amides I (n = 1 - 5), each combining the seco-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (seco-CBI) and pyrrolo[2,1-c][1,4]benzodiazepine (PBD) pharmacophores, was designed and prepared I were anticipated to cross-link between N3 of adenine and N2 of guanine in the minor groove of DNA. The compds., which differ in the chain length separating the two alkylation subunits, and the configuration of the CBI portion, showed great variation in cellular toxicity (over 4 orders of magnitude in a cell line panel) with the most potent example exhibiting IC50s in the pM range. Cytotoxicity correlated with the ability of I to cross-link naked DNA. Crosslinking was also observed in living cells, at much lower concns. than for a related sym. PBD dimer. A thermal cleavage assay was used to assess sequence selectivity, demonstrating that the CBI portion controlled the alkylation sites, while the PBD substituent increased the overall efficiency of alkylation. Several compds. were tested for in vivo activity using a tumor growth delay assay against WiDr human colon carcinoma xenografts, with (S,S)-I (n = 5) (the most cytotoxic and most efficient cross-linker) showing a statistically significant increase in survival time following a single iv dose.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202462 HCAPLUS
DOCUMENT NUMBER: 138:226761
TITLE: Synergistic anticancer combinations containing 5,6-dimethylxanthenone-4-acetic acid
INVENTOR(S): **Wilson, William Robert; Siim, Bronwyn Gae**
PATENT ASSIGNEE(S): Cancer Research Technology Limited, UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020259	A2	20030313	WO 2002-GB4025	20020903
WO 2003020259	A3	20030417		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1423105 A2 20040602 EP 2002-758562 20020903
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: GB 2001-21285 A 20010903
WO 2002-GB4025 W 20020903

AB The present invention relates to synergistic combinations of the 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and a compound selected from platinum compds., Vinca alkaloids, alkylating agents, anthracyclines, topoisomerase I inhibitors, antimetabolites and topoisomerase II inhibitors, which have antitumor activity. More particularly, the invention is concerned with the use of such combinations in the treatment of cancer and pharmaceutical compds. containing the combinations. The antitumor activity and host toxicity of DMXAA/cytotoxic drug combinations was assessed by varying the dose of chemotherapeutic drug up to the toxicity limit, with co-administration of a fixed DMXAA dose (80 μmol/kg, ca. 80% of MTD), and evaluating subsequent tumor growth delay. Of the 7 drugs investigated, 4 (doxorubicin, 5-fluorouracil, cyclophosphamide and cisplatin) had appreciable activity against this tumor as indicated by dose-response relationships providing significant slopes by linear regression, and highly significant growth delays of 10 days at their MTDs.

L18 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:13579 HCAPLUS
DOCUMENT NUMBER: 139:254741
TITLE: Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA)
AUTHOR(S): **Siim, Bronwyn G.**; Lee, Alan E.; Shalal-Zwain, Sahar; Pruijn, Frederik B.; **Wilson, W. R.**; **Sim, B. G.**; McKeage, M. J.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Experimental Oncology Group, The University of Auckland, Auckland, N. Z.
SOURCE: Cancer Chemotherapy and Pharmacology (2003), 51(1), 43-52
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose was to determine whether there is a therapeutic interaction between the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and nine chemotherapy drugs against an early-passage mouse mammary tumor (MDAH-MCa-4), and to investigate the mechanism of any such interaction. Female C3H/HeN mice bearing i.m. MDAH-MCa-4 tumors were injected i.p. with DMXAA (80 μmol/kg) or chemotherapy drug (at a range up to the maximum tolerated dose) alone, or coadministered. A small reduction in the dose of the chemotherapy drug was required in most cases, but the increase in antitumor effect was much greater than the increase in host toxicity (body weight loss). The therapeutic gain increased in the order 5-fluorouracil (no gain) < (etoposide, carboplatin, cyclophosphamide, doxorubicin, cisplatin) < (docetaxel, vincristine) < paclitaxel. The interaction with paclitaxel (31.6 μmol/kg) was striking, with coadministration of DMXAA extending the median tumor growth delay from 0.3 to 80 days with three of seven

animals cured. The interaction showed a broad timing of the optimum with similar activity when paclitaxel was administered 4 h before to 1 h after DMXAA. No therapeutic synergy was obtained when paclitaxel was combined with the antivascular agent combretastatin A4 phosphate (227 μmol/kg), which induced only transient blood flow inhibition in this tumor, measured using the H33342 perfusion marker. Paclitaxel did not enhance the antivascular activity of DMXAA. Plasma and tumor concns. of paclitaxel (and carboplatin), measured by LC-MS and ICP-MS resp., were not elevated by combination with DMXAA. There was a dramatic therapeutic interaction between DMXAA and standard chemotherapy drugs, particularly paclitaxel, against the MDAH-MCa-4 tumor, which was not due to a pharmacokinetic interaction or potentiation of antivascular activity. It is suggested that the major mechanism of synergy is killing of cells by DMXAA in poorly perfused regions of tumors that are inaccessible to chemotherapy drugs.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:667394 HCAPLUS
DOCUMENT NUMBER: 136:181
TITLE: Hypoxia-Selective Antitumor Agents. 16. Nitroarylmethyl Quaternary Salts as Bioreductive Prodrugs of the Alkylating Agent Mechlorethamine
AUTHOR(S): Tercel, Moana; Lee, Alan E.; Hogg, Alison; Anderson, Robert F.; Lee, Ho H.; **Siim, Bronwyn G.**; Denny, William A.; **Wilson, William R.**
CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2001), 44(21), 3511-3522
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:181

AB Nitrobenzyl quaternary salts of nitrogen mustards have been previously reported as hypoxia-selective cytotoxins. In this paper we describe the synthesis and evaluation of a series of heterocyclic analogs, including pyrrole, imidazole, thiophene, and pyrazole examples, chosen to cover a range of one-electron reduction potentials (from -277 to -511 mV) and substitution patterns. All quaternary salt compds. were less toxic in vitro than mechlorethamine, and all were more toxic under hypoxic than aerobic conditions, although the differentials were highly variable within the series. The most promising analog, N,N-Bis(2-chloroethyl)-N-methyl-N-[(1-methyl-4-nitro-5-imidazolyl)methyl]ammonium chloride (I), demonstrated DNA crosslinking selectively in hypoxic RIF-1 cells, and was active in vivo in combination with radiation or cisplatin. However, I also produced unpredictable toxicity in vivo, suggestive of nonspecific nitrogen mustard release, and this has restricted further development of these compds. as hypoxia-selective cytotoxins.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:758709 HCAPLUS
DOCUMENT NUMBER: 135:55392
TITLE: Pharmacokinetics and metabolism of the nitrogen mustard bioreductive drug 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (SN 23862) and

the corresponding aziridine (CB 1954) in KHT tumour-bearing mice

AUTHOR(S): Kestell, Philip; Pruijn, Frederik B.; **Siim, Bronwyn G.**; Palmer, Brian D.; **Wilson, William R.**

CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland, Auckland, 92019, N. Z.

SOURCE: Cancer Chemotherapy and Pharmacology (2000), 46(5), 365-374
CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacokinetics and metabolism was characterized in mice of 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (SN 23862), the lead compound of a new class of bioreductive drugs in which a nitrogen mustard is activated by nitroredn. Comparison is made with the corresponding aziridine derivative CB 1954. Male C3H/HeN mice, bearing s.c. were used. KHT tumors, received 3H-labeled SN 23862 or CB 1954 i.v. at 200 μmol/kg. Blood plasma, urine, and tumor samples were assayed for total radioactivity, and for parent compds. by HPLC. Metabolites were identified by 1H-NMR and mass spectrometry. Cytotoxicity of compds. against Chinese hamster AA8 cells was determined by growth inhibition assay. The plasma pharmacokinetics of SN 23862 and CB 1954 were similar, with half-lives of 1.1 and 1.2 h, resp. SN 23862 provided tumor/plasma ratios and absolute tumor AUC values almost 2 times higher than CB 1954. Despite this, SN 23862 was more extensively metabolized than CB 1954, the major route being sequential oxidative dechloroethylation of the nitrogen mustard moiety to the relatively non-toxic half mustard and 5-amine. The inferred chloroacetaldehyde co-product was 260 times more potent than SN 23862. A tetrahydroquinoxaline metabolite resulting from reduction of the 4-nitro group followed by intramol. alkylation was weakly cytotoxic, while the more cytotoxic 2-amino derivative of SN 23862 was detected in trace amts. CB 1954 was metabolized by analogous pathways, but the 4- and 2-amine nitroredn. products were the major metabolites while oxidative dealkylation was minor. The lesser propensity for SN 23862 to undergo nitroredn. in the host, relative to CB 1954, argues that dinitrobenzamide mustards may be preferable to the corresponding aziridines as bioreductive prodrugs for cancer treatment. However, the toxicol. significance of oxidative metabolism of the bis(2-chloroethyl)amine moiety needs to be addressed.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:642218 HCAPLUS

DOCUMENT NUMBER: 133:307155

TITLE: Scintigraphic imaging of the hypoxia marker 99mtechnetium-labeled 2,2'-(1,4-diaminobutane)bis(2-methyl-3-butanone) dioxime (99mTc-labeled HL-91; Prognox): noninvasive detection of tumor response to the antivascular agent 5,6-dimethylxanthenone-4-acetic acid

AUTHOR(S): **Siim, Bronwyn G.**; Laux, Wilda T.; Rutland, Michael D.; Palmer, Barry N.; **Wilson, William R.**

CORPORATE SOURCE: Department of Pathology and Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.

SOURCE: Cancer Research (2000), 60(16), 4582-4588

CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) and combretastatin A4 phosphate (CA-4-P) markedly inhibit tumor blood flow in mice and are both currently in clin. trial. One of the challenges in clin. evaluation of antivascular agents is the monitoring of tumor blood flow inhibition in individual patients. This study investigates, using mouse models, whether a new marker for tissue hypoxia, 99mtechnetium-labeled 2,2'-(1,4-diaminobutane)bis(2-methyl-3-butanone) dioxime (99mTc-labeled HL-91; Prognox)] has potential for the scintigraphic monitoring of tumor response to antivascular agents. Determination of radioactivity in dissected tissues 3 h after DMXAA (80 μmol/kg) or CA-4-P (227 μmol/kg) was injected indicated that both drugs inhibited blood flow (86RbCl uptake; 84 and 87%, resp.) and increased 99mTc-labeled HL-91 levels (350 and 300%, resp.) selectively in murine RIF-1 tumors. Planar imaging of 99mTc-labeled HL-91 3 h after DMXAA injection showed a dose-dependent increase in tumor levels above a threshold of 50 μmol/kg; this same threshold was observed for the inhibition of tumor blood flow (determined using Hoechst 33342). DMXAA also inhibited blood flow-and increased 99mTc-labeled HL-91 uptake-in MDAH-MCa-4 mouse mammary carcinomas and in NZMN10 human melanoma xenografts. Whether 99mTc-labeled HL-91 might also be useful as a biomarker for tumor cell killing was investigated by clonogenic assay of surviving cells 15 h after imaging 99mTc-labeled HL-91 in RIF-1 tumors. Log cell kill in individual tumors showed a statistically significant linear correlation ($P < 0.001$) with 99mTc-labeled HL-91 uptake after 60 μmol/kg ($r2 = 0.79$) and 70 μmol/kg ($r2 = 0.44$) but not at 80 μmol/kg DMXAA. The lack of correlation at high doses presumably reflects the insensitivity of the tumor-averaged 99mTc-labeled HL-91 signal to small regions in which tumor blood flow is preserved (which will limit log cell kill). The results indicate the potential of 99mTc-labeled HL-91 for the noninvasive imaging of tumor blood flow inhibition by antivascular drugs in humans.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:621995 HCAPLUS
DOCUMENT NUMBER: 133:344161
TITLE: Comparison of aromatic and tertiary amine N-oxides of acridine DNA intercalators as bioreductive drugs. Cytotoxicity, DNA binding, cellular uptake, and metabolism
AUTHOR(S): **Siim, B. G.**; Hicks, K. O.; Pullen, S. M.; van Zijl, P. L.; Denny, W. A.; **Wilson, W. R.**
CORPORATE SOURCE: Department of Pathology, Section of Oncology, The University of Auckland, Auckland, N. Z.
SOURCE: Biochemical Pharmacology (2000), 60(7), 969-978
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Some N-oxide derivs. of DNA intercalators are bioreductive prodrugs that are selectively toxic under hypoxic conditions. The hypoxic selectivity is considered to result from an increase in DNA binding affinity when the N-oxide moiety is reduced. This study investigated whether differences in DNA binding affinity between N-oxides and their corresponding amines, measured by equilibrium dialysis, can account for the hypoxic cytotoxicity ratios (HCR) of tertiary amine N-oxide (-tO) and aromatic N-oxide (-aO)

derivs. of the 1-nitroacridine nitracrine (NC) and its non-nitro analog 9-[3-(N,N-dimethylamino)propylamino]acridine (DAPA). Cytotoxicity was measured in aerobic and hypoxic suspensions of Chinese hamster ovary (CHO) AA8 cells by clonogenic assay. HCR were much greater for NC-tO (820-fold) than for NC (5-fold) or NC-aO (4-fold), whereas DAPA and its N-oxides lacked hypoxic selectivity (1-fold). DNA binding measurements demonstrated that binding affinity is lowered more by aromatic than tertiary amine (side-chain) N-oxides, an observation that does not correlate with HCR. Compds. were accumulated in cells to high concns. (Ci/Ce ≈ 10-200), with the exception of the tertiary amine N-oxides, for which the ratio of intracellular to extracellular drug was less than unity. For NC-tO this probably resulted from low pKa values for both the acridine chromophore and the side-chain, whereas DAPA-tO may be too hydrophilic for efficient membrane permeation. Bioreductive drug metabolism, assessed by HPLC, was faster for the NC than the DAPA N-oxides. The high HCR of NC-tO relative to NC-aO is ascribed to the rapid and selective reduction of its N-oxide moiety, followed by activation of the NC intermediate by O2-sensitive reduction of its 1-nitro group to the corresponding 1-amine. The metabolism studies suggest that unmasking of DNA binding affinity by reductive removal of the N-oxide moiety, although not the only determinant, is important and needs to occur before nitroredn. for optimal effect.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:5894 HCAPLUS
DOCUMENT NUMBER: 130:206765
TITLE: Enhancement of tumor radiation response by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid
AUTHOR(S): **Wilson, William R.**; Li, Alan E.; Cowan, David S. M.; **Siim, Bronwyn G.**
CORPORATE SOURCE: Section of Oncology, Department of Pathology, The University of Auckland, Auckland, N. Z.
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1998), 42(4), 905-908
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) selectively damages tumor vasculature and is currently in clin. trial as an antitumor agent. Its ability to induce synthesis of tumor necrosis factor (TNF), and its apparent selectivity for poorly-perfused regions in tumors, suggests it possible use in combination with radiotherapy. This investigation examines activity of DMXAA as a radiation modifier using two murine tumors. Tumor growth delay was evaluated using i.m. RIF-1 and MDAH-MCa-4 tumors irradiated in unanaesthetized, restrained mice (cobalt-60) using single dose or multiple fractions (8 + 2.5 Gy over 4 days) with DMXAA administered i.p. at various times in relation to irradiation Administration of DMXAA (80 μmol/kg, i.p.) immediately after radiation resulted in a large increase in tumor growth delay, giving a radiation dose modifying factor of 2.3 for RIF-1 and 3.9 for MDAH-MCa-4. The combination was less active when radiation was given 1-4 h after DMXAA, but was highly active 12-48 h after DMXAA. At the latter times, clamping the tumor blood supply caused a large increase in radioresistance. These studies suggest that cells surviving DMXAA are hypoxic for only a short period. DMXAA increased overall growth delay when administered daily during fractionated irradiation, giving an approx. additive response. The marked synergy between DMXAA and single dose ionizing radiation may

reflect the complementarity of these agents at the microregional level, with DMXAA preferentially killing hypoxic cells in poorly perfused regions. Despite addnl. hypoxia shortly after DMXAA treatment, surviving cells appear to reoxygenate quickly which makes it feasible to use DMXAA before and during fractionated radiotherapy. The combination of fractionated radiation and DMXAA appears to be less effective than for single dose radiation (possibly because of the smaller contribution of hypoxia under these conditions), but may be therapeutically useful.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:741284 HCAPLUS
DOCUMENT NUMBER: 130:133611
TITLE: Extravascular diffusion of tirapazamine: effect of metabolic consumption assessed using the multicellular layer model
AUTHOR(S): Hicks, Kevin O.; Fleming, Yvette; **Siim, Bronwyn G.**; Koch, Cameron J.; **Wilson, William R.**
CORPORATE SOURCE: Section of Oncology, Department of Pathology, The University of Auckland, Auckland, N. Z.
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1998), 42(3), 641-649
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypoxia-selective cytotoxic agents, like tirapazamine (TPZ), must diffuse considerable distances in tumors to reach their target cell population. This study uses a new three-dimensional tissue culture model, in which cells are grown as multicellular layers (MCL), to investigate whether metabolic consumption of TPZ is sufficiently rapid to compromise its extravascular diffusion in tumors. V79-171b and MGH-U1 cells were grown as MCL to thicknesses of approx. 120 and 360 μm resp. The extent of hypoxia in MCL, as assessed by EF5 binding, was modulated by altering gas-phase O2 content, and flux of TPZ through MCL was investigated by high-performance liquid chromatog. (HPLC). Data were fitted to a diffusion-reaction math. model to determine the diffusion coefficient of TPZ in the MCL (DM) and the rate of its metabolic consumption under anoxia. These parameters were used to simulate TPZ transport in tumors. The flux of TPZ through well-oxygenated MCL (equilibrated with 95% O2) was well fitted as Fickian diffusion without reaction, with a DM of 7.4+10-7 cm2s-1 (12-fold lower than in culture medium) for V79 and 1.3+10-6 cm2s-1 for MGH-U1 MCL. Flux of TPZ was suppressed under anoxia, and fitting the data required inclusion of a reaction term with a rate constant for metabolic consumption of TPZ of 0.52 min-1 for V79 and 0.31 min-1 for MGH-U1 MCL. These transport parameters would translate into a 43% or 30% decrease resp. in TPZ exposure, as a result of drug metabolism, in the center of a slab of anoxic tissue 100 μm in thickness. MCL cultures provide an in vitro model for investigating the interaction between metabolic consumption and diffusion of bioreductive drugs. If rates of diffusion and metabolism similar to those measured in V79 and MGH-U1 MCL apply in tumors, then cells in large confluent regions of hypoxia would be partially protected by failure of TPZ penetration. Simulation of extravascular transport of TPZ-like bioreductive drugs demonstrates that the optimum metabolic rate constant is determined by two competing requirements:
it should be high enough to ensure potent cytotoxicity under hypoxia, yet low enough that penetration is not severely compromised.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:145311 HCAPLUS
DOCUMENT NUMBER: 128:238843
TITLE: Nitro reduction as an electronic switch for bioreductive drug activation
AUTHOR(S): **Siim, Bronwyn G.**; Denny, William A.; **Wilson, William R.**
CORPORATE SOURCE: Section of Oncology, Department of Pathology, The University of Auckland, Auckland, N. Z.
SOURCE: Oncology Research (1997), 9(6/7), 357-369
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 86 refs. It is well known that the reduction of aromatic nitro groups can give rise to toxic species, and that net nitro reduction by one-electron reductases can usually be inhibited by oxygen. There has been much interest in utilizing this biotransformation to activate drugs in hypoxic regions of tumors, but no clin. useful compound has yet resulted. Nitroreductive activation of prodrugs by oxygen-insensitive (and oxygen-sensitive) reductases is also of current interest because of new methods for introducing specific nitroreductases into tumors (e.g., as antibody-enzyme conjugates or by gene therapy). In most of the compds. investigated previously, cytotoxicity appears to be due to reactive nitroso or hydroxylamine reduction products arising from the nitro group itself. It is argued that there is greater scope for designing potent and selective nitro compds. by using the nitro group as an electronic switch to activate a latent reactive moiety elsewhere in the mol. Examples of this approach include the nitro(hetero)aromatic mustards (e.g., SN 23816, NSC 646394) in which the nitro group controls the reactivity of a nitrogen mustard to which it is directly conjugated, and the nitro(hetero)aromatic methylquaternary (NMQ) mustards (e.g., SN 25341, NSC 658926) in which reduction of the nitro group triggers fragmentation of the mol. to release a reactive aliphatic nitrogen mustard. Many of these compds. show very high selectivity for hypoxic cells in culture. Some are also active against hypoxic cells in tumors, and provide large tumor growth delays when combined with tumor blood flow inhibitors such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA). These prodrug designs also have potential for releasing effectors other than nitrogen mustards, which opens up many possibilities for use of nitro compds. as tumor-selective prodrugs.
REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:231023 HCAPLUS
DOCUMENT NUMBER: 126:258476
TITLE: Hypoxiaselective Antitumor Agents. 15. Modification of Rate of Nitroreduction and Extent of Lysosomal Uptake by Polysubstitution of 4-(Alkylamino)-5-nitroquinoline Bioreductive Drugs
AUTHOR(S): **Siim, Bronwyn G.**; Atwell, Graham J.; Anderson, Robert F.; Wardman, Peter; Pullen, Susan M.; **Wilson, William R.**; Denny, William A.
CORPORATE SOURCE: Cancer Research Laboratory Section of Oncology Department of Pathology, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Journal of Medicinal Chemistry (1997), 40(9),

1381-1390
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies have shown that 4-(alkylamino)-5-nitroquinolines possess high selectivity (20-60-fold) for hypoxic tumor cells in vitro, but are not active as hypoxia-selective cytotoxins (HSCs) in vivo. The compds. show inadequate rates of extravascular diffusion, likely due both to sequestration of the bisbasic compds. into lysosomes and rapid nitroredn. A further series of analogs, designed to counteract these limitations, has been synthesized and evaluated. Analogs bearing one to three electron-donating substituents on the quinoline have one-electron reduction potentials up to 100 mV lower than that of the unsubstituted compound, but do not have improved biol. activity. The relation between hypoxic selectivity and rates of metabolic reduction suggests at least two mechanisms of cytotoxicity for this series of 5-nitroquinolines. Compds. with high rates of reduction are toxic via oxygen-sensitive net bioredn., while compds. which are poor substrates for nitroredn. are toxic through an oxygen-insensitive non-bioreductive mechanism. As rates of metabolic reduction are lowered, the non-bioreductive mechanism of toxicity becomes dominant and hypoxic selectivity is lost. A small series of analogs bearing hydrophilic but neutral side chains were also prepared Compds. with a dihydroxypropyl side chain retained cytotoxic potency and hypoxic cell selectivity in cell culture assays, and had lowered uptake into lysosomes, but none of three analogs evaluated against KHT tumors in mice showed activity as an HSC in vivo.

L18 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:679717 HCAPLUS
DOCUMENT NUMBER: 123:131925
TITLE: Efficient redox cycling of nitroquinoline bioreduction drugs due to aerobic nitroreduction in Chinese hamster cells
AUTHOR(S): **Siim, Bronwyn G.; Wilson, William R.**
CORPORATE SOURCE: Dep. Pathology, Univ. Auckland, Auckland, N. Z.
SOURCE: Biochemical Pharmacology (1995), 50(1), 75-82
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitroquinoline bioreductive drugs with 4-alkylamino substituents undergo one-electron reduction in mammalian cells, resulting in futile redox cycling due to oxidation of the nitro radical anion in aerobic cultures, and eventual reduction to the corresponding amines in the absence of oxygen. Rates of drug-induced oxygen consumption (R) due to redox cycling in cyanide-treated AA8 cell cultures were determined for 17 nitroquinolines. There was a linear dependence of log R on the one-electron reduction potential at pH 7 (E7) with a slope of 7.1 V-1, excluding compds. with substituents ortho to the nitro group. The latter had anomalously low rates of oxygen consumption relative to E71, suggesting that interaction with the active site of nitroreductases is impeded sterically for such compds. Absolute values of R (and the observed E71 dependence) were well predicted by a simple kinetic model that used rates of net nitroredn. to the amines under anoxia as a measure of the rates of one-electron reduction in aerobic cells. This indicates that redox cycling of 4-alkylaminonitroquinolines occurs at high efficiency in aerobic cells, suggesting that there are no quant. significant fates of nitro radical anions in cells other than their reaction with oxygen (or their spontaneous disproportionation under hypoxia).

L18 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:201565 HCAPLUS
DOCUMENT NUMBER: 122:314
TITLE: Oxygen dependence of the cytotoxicity and metabolic activation of 4-alkylamino-5-nitroquinoline bioreductive drugs
AUTHOR(S): **Siim, B. G.**; Atwell, G. J.; **Wilson, W. R.**
CORPORATE SOURCE: Department Pathology, University Auckland School Medicine, Auckland, N. Z.
SOURCE: British Journal of Cancer (1994), 70(4), 596-603
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cytotoxic potency of 4-alkylamino-5-nitroquinoline drugs in AA8 cell cultures is enhanced up to 60-fold under hypoxia, with wide variations in selectivity for hypoxic cells observed for different members of this series. This study uses three representative 5-nitroquinolines to examine whether these differences in hypoxia-selective cytotoxicity are cell line specific, and to explore quant. the oxygen dependence of the cytotoxicity and metabolism of these compds. The parent compound 5NQ, its 8-Me analog (8Me-5NQ) and the 8-methylamino analog (8NHMe-5NQ) each showed similar hypoxic selectivity (ratio of concentration x time for 90% kill for zero vs. 20% oxygen of 13-18-, 30-69- and 1.2-1.4-fold resp. in the three cell lines tested (AA8 Chinese hamster ovary, EMT6/Ak mouse mammary tumor and FME human melanoma)). The cytotoxicity and metabolism (covalent binding) of radiolabeled 8Me-5NQ was investigated in AA8 cultures over a range of oxygen tensions (0-95%). The oxygen tension in solution required for 50% inhibition of log cell kill or adduct formation observed under anoxia (C50) was 0.01 and 0.02% oxygen resp., suggesting that bioreductive alkylation is the mechanism of 8Me-5NQ toxicity. The K-value (oxygen concentration for cytotoxic potency equal to the mean of the potencies at zero and infinite oxygen) was similar (0.02% oxygen). Calcns. based on measured rate consts. for formation of the nitroradical anion of 8Me-5NQ and rates of radical loss through disproportionation or reaction with oxygen, predict a K-value for 8Me-5NQ of 0.025% oxygen, in good agreement with the exptl. determined value. Modeling of cell killing expected by the combination of 8Me-5NQ plus radiation suggested that tumor cells at intermediate oxygen tensions (0.01-1%) will be partially resistant to this treatment, and would limit the use of these 5-nitroquinolines in combination with radiation, unless sufficient drug could be delivered to cause extensive killing in the anoxic compartment.

L18 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:199501 HCAPLUS
DOCUMENT NUMBER: 122:255640
TITLE: Metabolic and radiolytic reduction of 4-alkylamino-5-nitroquinoline bioreductive drugs. Relationship to hypoxia-selective cytotoxicity
AUTHOR(S): **Siim, Bronwyn G.**; Atwell, Graham J.; **Wilson, William R.**
CORPORATE SOURCE: Department of Pathology, University of Auckland School of Medicine, Auckland, N. Z.
SOURCE: Biochemical Pharmacology (1994), 48(8), 1593-604
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 4-alkylamino-5-nitroquinolines (5NQs) are a new series of bioreductive drugs that exhibit varying degrees of selective toxicity (up to 60-fold) under hypoxic conditions. The products of reduction of six 5NOs were characterized and rates of reduction compared in aerobic and hypoxic AA8 cells. The major stable product of both radiolytic and metabolic reduction under anoxic conditions were the corresponding amines, which were not responsible for the toxicity of the parent nitro compds. Metabolism of each compound was inhibited completely in aerobic cells, indicating that differences in hypoxia-selective toxicity in this series are not due to variations in efficiency as substrates for oxygen-insensitive nitro reduction Rates of hypoxic metabolism correlated broadly with hypoxia-selective cytotoxicity; the 5NQ derivs. with high rates of hypoxic metabolism had good hypoxia-selective cytotoxicity, whereas the compds. with low rates of reduction (the 3,6-di-Me and 8-methylamino compds.; 3,6diMe-5NQ and 8NHMe-5NQ) were non-selective. Low rates of drug-induced oxygen consumption by 3,6diMe-5NQ and 8NHMe-5NQ in respiration-inhibited cells confirmed that these compds. are poor substrates for enzymic nitro reduction While there was an overall correlation between one-electron reduction potential at pH 7 (E1/7) and rate of metabolic reduction, the relatively high E1/7 of 3,6diMe-5NQ (-367 mV) indicates that rates of reduction, and hypoxic selectivity of cytotoxicity, cannot be predicted from reduction potential alone. 3,6DiMe-5NQ and 8NHMe-5NQ are cytotoxic through a non-bioreductive mechanism, the variable contribution of which may underlie the differences in hypoxia-selective cytotoxicity within this series of bioreductive drugs.

L18 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:621176 HCAPLUS
DOCUMENT NUMBER: 121:221176
TITLE: Does DNA targeting affect the cytotoxicity and cell uptake of basic nitroquinoline bioreductive drugs?
AUTHOR(S): **Siim, Bronwyn G.**; Denny, William A.; **Wilson, William R.**
CORPORATE SOURCE: Sch. Med., Univ. Auckland, Auckland, N. Z.
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1994), 29(2), 311-15
CODEN: IOBPD3; ISSN: 0360-3016
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of 4-(N,N-dimethylaminopropylamino)-5-nitroquinoline bioreductive drugs was studied to determine whether DNA binding influences cytotoxic potency, hypoxic selectivity or cellular uptake in cell culture. Cytotoxicity was assessed by clonogenic assay of stirred suspension cultures of aerobic or hypoxic late-log-phase AA8 cells. Drug uptake was measured by HPLC of MeCN-extracted cell pellets and extracellular medium, or by using radiolabeled drug. Drug binding to calf thymus DNA was measured by equilibrium dialysis. The compds. were weak DNA binders under physiol. conditions, with association consts. in the range 25-480 M-1. There was no correlation between DNA binding affinity and hypoxic or aerobic cytotoxic potency, or hypoxic selectivity. These compds. were accumulated by cells to high concns. (25-60-fold higher than extracellular), but cell uptake also showed no relationship to DNA-binding affinity. NH4Cl selectively raised intralysosomal pH and inhibited the cellular accumulation of these drugs. These results indicate that DNA binding is not the major determinant of cytotoxic potency, hypoxic selectivity, or cellular uptake of the 5-nitroquinolines. Instead, the variable contribution of a nonbioreductive mechanism of toxicity appears to underlie the differences in cytotoxic potency and hypoxic selectivity within this series. The high intracellular drug concns. of these diprotic bases appear to be due primarily to lysosomal uptake rather than DNA binding. Lysosomal uptake might restrict diffusion of basic bioreductive drugs to the target hypoxic

regions of solid tumors.

L18 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:587412 HCAPLUS
DOCUMENT NUMBER: 117:187412
TITLE: 5-Nitro-4-(N,N-dimethylaminopropylamino)quinoline (5-nitraquine), a new DNA-affinic hypoxic cell radiosensitizer and bioreductive agent: comparison with nitracrine
AUTHOR(S): **Wilson, William R.**; **Siim, Bronwyn G.**; Denny, William A.; Van Zijl, Pierre L.; Taylor, Maryann L.; Chambers, Dawn M.; Roberts, Peter B.
CORPORATE SOURCE: Sch. Med., Univ. Auckland, Auckland, N. Z.
SOURCE: Radiation Research (1992), 131(3), 257-65
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Targeting of electron-affinic radiosensitizers to DNA via noncovalent binding (e.g., intercalation) may offer the potential for increasing sensitizing efficiency. However, it has been suggested that high-affinity DNA binding may compromise sensitization by restricting the mobility of sensitizers along the DNA, and by decreasing rates of extravascular diffusion in tumors. The weak DNA intercalator nitracrine (1-NC) is a more efficient radiosensitizer than related nitroacridines with higher DNA-binding affinities. The present study investigates whether electron-affinic agents of even lower DNA-binding affinity may be superior to nitroacridines. The quinoline analog of 1-NC, 5-nitraquine (5-NQ), was shown to have an intrinsic association constant for calf thymus DNA in 20 mM phosphate buffer which was 12-fold lower than that of 1-NC. 5-Nitraquine was not accumulated as efficiently as 1-NC by AA8 cells but, despite a similar one-electron reduction potential, was 2-3-fold more potent than 1-NC as a hypoxia-selective radiosensitizer in vitro when compared on the basis of average intracellular concentration Thus, the radiosensitizing potency of 5-NQ appears not to be compromised by its low DNA-binding affinity. The cytotoxic mechanisms of 5-NQ and 1-NC appear to be similar (hypoxia-selective formation of DNA monoadducts), but 5-NC is 1200-fold less potent than 1-NC as a cytotoxin. Despite this advantage, 5-NQ was not active in vivo as a radiosensitizer in SCCVII tumors. This lack of activity appears to be due to its relatively high toxicity in vivo (i.p. LD50 of 105 μmol/kg in C3H/HeN mice), high one-electron reduction potential (-286 mV), and rapid metabolism to the corresponding amine in mice. The in vitro therapeutic index (hypoxic radiosensitizing potency/aerobic cytotoxic potency) of this weak DNA binder was lower than that of the non-DNA targeted radiosensitizer misonidazole, suggesting that DNA targeting enhances cytotoxicity more than radiosensitization. Development of useful DNA-targeted radiosensitizers may require the exploitation of DNA binding modes different from those of the nitroacridines and nitroquinolines.

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                "CANCER RESEARCH TECHNOLOGY LTD"/PA OR "CANCER RESEARCH
                TECHNOLOGY LTD UK"/PA)


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L36  ANSWER 1 OF 36  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:696360  HCAPLUS
DOCUMENT NUMBER:          141:225492
TITLE:                    Preparation of isoxazoles as inhibitors of heat shock
                          proteins
INVENTOR(S):              Drysdale, Martin James; Dymock, Brian William; Finch,
                          Harry; Webb, Paul; Mcdonald, Edward; James, Karen
                          Elizabeth; Cheung, Kwai Ming; Mathews, Thomas Peter
PATENT ASSIGNEE(S):       Vernalis Cambridge Limited, UK; Cancer Research
                          Technology Ltd; The Institute of Cancer Research;
                          et al.
SOURCE:                   PCT Int. Appl., 180 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
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     WO 2004072051          A1    20040826    WO 2004-GB506            20040209
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             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
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MZ, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

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GB 2003-6560 A 20030321
GB 2003-13751 A 20030613

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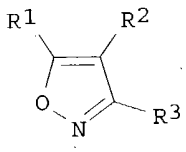

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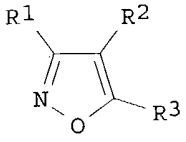


II

AB Title compds. [I, II; R1 = Ar1(Alk1)p(Z)r(Alk2)sQ; Ar1 = (substituted) aryl, heteroaryl; Alk1, Alk2 = (substituted) alkylene, alkenylene; p, r, s = 0, 1; Z = O, S, CO, CS, SO2, CO2, CONRA, CSNRA, SO2NRA, NRACO, NRASO2, NRA; RA = H, alkyl; Q = H, (substituted) carbocyclyl, heterocyclyl; R2 = Ar1(Alk1)p(Z)r(Alk2)sQ, carboxamide, carbocyclyl, heterocyclyl optionally substituted by (Alk1)pZr(Alk2)sQ; R3 = H, (substituted) cycloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, carboxyl, carboxamide, carboxyl ester], were prepared Thus, NH2OH.HCl and 7-hydroxy-3-(4-methoxyphenyl)-2-methylchromen-4-one (preparation given) were refluxed 4 h in pyridine to give 4-[4-(4-methoxyphenyl)-3-methylisoxazol-5-yl]benzene-1,3-diol. The latter in the Malachite Green ATPase assay inhibited HSP90 with IC50 <50 μM.

L36 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:550875 HCAPLUS
DOCUMENT NUMBER: 141:106370
TITLE: Preparation of 4-[1-(sulfonyl)-1H-indol-2-yl]-4-(hydroxy)-cyclohexa-2,5-dienone compounds and analogs thereof as therapeutic agents
INVENTOR(S): Stevens, Malcolm Francis Graham; Westwell, Andrew David; Poole, Tracey Dawn; Wells, Geoffrey; Berry, Jane Marie
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056361	A1	20040708	WO 2002-GB5842	20021220

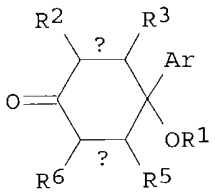
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2002-GB5842 20021220

OTHER SOURCE(S): MARPAT 141:106370

GI



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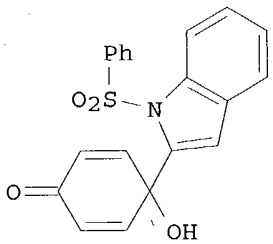


II

AB This invention pertains to certain 4-(1-(sulfonyl)-1H-indol-2-yl)-4-(hydroxy)-cyclohexa-2,5-dienone compds., and analogs thereof, including compds. of the formula I [wherein Ar = 1-(sulfonyl)-1H-indol-2-yl; the bond marked α is a single bond or a double bond; the bond marked β is a single bond or a double bond; OR1 = OH, ether group (e.g., OMe) or acyloxy (i.e., reverse ester) group (e.g., -OC(O)Me); R2, R3, R5, R6 = H, monovalent monodentate substituent or a ring substituent which, together with an adjacent ring substituent, and together with the ring atoms to which these ring substituents are attached, form a fused ring; and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof] which are, inter alia, antiproliferative agents, anticancer agents, and/or thioredoxin/thioredoxin reductase inhibitors. Syntheses of 11 representative compds. I are described. Thus, reacting 4,4-dimethoxycyclohexa-2,5-dienone (preparation given) with 1-benzenesulfonyl-1H-indole afforded 18% II 4-(1-benzenesulfonyl-1H-indol-2-yl)-4-hydroxycyclohexa-2,5-dienone which showed IC50 of 0.086 μM and 0.259 μM against HCT 116 and HT 29 growth (in vitro), resp. The present invention also pertains to pharmaceutical compns. comprising compds. I, and the use of such compds. I and compns., both in vitro and in vivo, for example, in the treatment of proliferative conditions, (e.g., cancer), and/or conditions mediated by thioredoxin/thioredoxin reductase.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:546484 HCAPLUS

DOCUMENT NUMBER: 141:106462

TITLE: Preparation of pyrazoles as inhibitors of HSP90

INVENTOR(S): Beswick, Mandy Christine; Drysdale, Martin James; Dymock, Brian William; McDonald, Edward

PATENT ASSIGNEE(S): Vernalis Cambridge Limited, UK; **Cancer Research Technology Ltd.**; The Institute of Cancer Research

SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

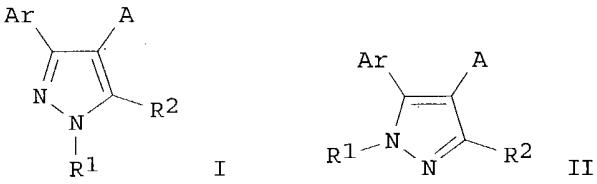
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004056782	A1	20040708	WO 2003-GB5501	20031218

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-29618 A 20021219
OTHER SOURCE(S): MARPAT 141:106462
GI



AB The title compds. [I or II; Ar = (un)substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl; R1 = H, alkyl; R2 = H, (un)substituted cycloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, carboxyl, carboxamide or carboxyl ester group; A = non-aromatic carbocyclic or heterocyclic ring wherein (i) a ring carbon is optionally substituted, and/or (ii) a ring nitrogen is optionally substituted by a group of formula -(Alk1)p(Cyc)n(Alk3)m(Z)r(Alk2)sQ where Alk1, Alk2 and Alk3 = alkyl; Cyc = carbocyclic or heterocyclic radical; m, n, p, r and s = 0-1; Z = O, S, CO, SO2, etc.; Q = H, (un)substituted carbocyclic or heterocyclic radical] which are inhibitors of HSP90, and are of value in the treatment of diseases responsive to HSP90 inhibition such as cancer, were prepared E.g., a multi-step synthesis of 4-chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)benzene-1,3-diol which showed IC50 of <50 μM in the malachite green ATPase assay, was given.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:490722 HCAPLUS
DOCUMENT NUMBER: 141:54321
TITLE: Preparation of 3-(2-hydroxyphenyl)-1H-pyrazole-4-carboxamides as HSP90 inhibitors for the treatment of cancer
INVENTOR(S): Beswick, Mandy Christine; Brough, Paul Andrew; Drysdale, Martin James; Dymock, Brian William
PATENT ASSIGNEE(S): Vernalis (Cambridge) Limited, UK; **Cancer Research Technology Ltd.**; The Institute of Cancer Research
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

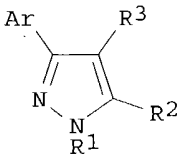
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050087	A1	20040617	WO 2003-GB5275	20031204

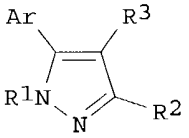
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-28417 A 20021205
OTHER SOURCE(S): MARPAT 141:54321
GI



I



II

AB Title compds. [I, II; Ar = (further substituted) 2-hydroxyaryl, 2-hydroxyheteroaryl; R1 = H, (substituted) alkyl; R2 = H, (substituted) cycloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, carboxyl, carboxamide, carboxyl ester group; R3 = carboxamide group], were prepared Thus, O-(7-azabenzotriazolyl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 3-(2,4-bisbenzyloxy-5-chlorophenyl)-1(2)-(2-trimethylsilylethoxymethyl)-1H-pyrazole-4-carboxylic acid (preparation given), 4-aminoacetophenone, and diisopropylethylamine were heated together in DMF at 100° for 5 min. using microwave heating and the mixture was kept 2 h at ambient temperature to give a residue which was stirred overnight with BCl3 in CH2Cl2 to give 3-(5-chloro-2,4-dihydroxyphenyl)-1H-pyrazole-4-carboxylic acid (4-acetylphenyl)amide. The latter showed IC50 <50 μM in the malachite green ATPase assay using yeast HSP90.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:467920 HCAPLUS
DOCUMENT NUMBER: 141:22215
TITLE: Neutralizing antibody to decay-accelerating factor
INVENTOR(S): Durrant, Gillian Lindy
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004048413	A2	20040610	WO 2003-GB5163	20031126
WO 2004048413	A3	20040729		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-27644 A 20021127

AB The author discloses an antibody which binds to SCR1 and SCR2 of CD55, neutralizing CD55, and makes cancer cells susceptible to complement mediated attack.

L36 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:453254 HCAPLUS
DOCUMENT NUMBER: 141:22212
TITLE: Inhibition of angiogenesis: Antibodies to magic roundabout
INVENTOR(S): Bicknell, Roy; Suchting, Steven; Stewart, Lorna Mary Dyet
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004046191	A2	20040603	WO 2003-GB5059	20031120
WO 2004046191	A3	20040729		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-27080 A 20021120
GB 2003-21401 A 20030912

AB The authors disclose a method of inhibiting angiogenesis comprising administering an antibody that selectively binds to the extracellular region of human magic roundabout (MR). In addition the authors disclose a method of inhibiting angiogenesis comprising administering the extracellular domain (residues 1-467) of MRNA. In one example,

endothelial cell migration and proliferation is inhibited by monoclonal antibody MR7 directed to human magic roundabout.

L36 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392594 HCAPLUS
DOCUMENT NUMBER: 140:402088
TITLE: Methods for screening agents modulating MAL activity and their therapeutic uses thereof
INVENTOR(S): Treisman, Richard Henry; Miralles-Arenas, Francisco; Zaromytidou, Alexia-Ileana; Posern, Guido
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039980	A1	20040513	WO 2003-GB4674	20031030

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-422420P P 20021030
AB The present invention relates to agents that modulate MAL (megacaryocytic acute leukemia protein) activity. Specifically, the invention discloses that agents that modulate the Rho-dependent SRF pathway by modulating a MAL activity through modulating MAL-SRF interactions; translocation of MAL to and/or from the nucleus; MAL C-terminal phosphorylation; MAL-actin interactions; MAL dimerization; or MAL gene expression. The invention further relates to pharmaceutical compns. containing these agents, and methods of treatment for disorders such as cancer, wounds, myopathies and diseases related to enhanced angiogenesis.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

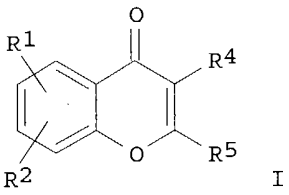
L36 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:363684 HCAPLUS
DOCUMENT NUMBER: 140:380636
TITLE: Oral anti-cancer composition of DMXAA and method of use
INVENTOR(S): Baguley, Bruce Charles; Ching, Lai-Ming; Kestell, Philip; Zhao, Liangli
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: Brit. UK Pat. Appl., 38 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2394658	A1	20040505	GB 2002-25508	20021101
WO 2004039363	A1	20040513	WO 2003-GB4688	20031030

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-25508 A 20021101
OTHER SOURCE(S): MARPAT 140:380636
GI



I

AB The present invention relates to the use of the compds. of formula I, where (a) R4 and R5 with the C atoms to which they are attached form a 6-membered aromatic ring having substituents -B-COOH (where B is a hydrocarbyl link) and R3 and R1, R2 and R3 are standard substituents; (b) each of R4 and R5 is H or optionally substituent Ph with the proviso only one is H, R1 is H, alkyl or alkoxy and R2 is B-COOH as above. A preferred compound is 5,6-dimethylxanthenone-4-acetic acid (DMXAA). The compds. are for the treatment of cancer, wherein the compds. are administered gastrointestinally, preferably orally. More particularly, the invention is concerned with the use of such compns., wherein the compound is delivered to the site of action in the patient to be treated in two or more doses.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:354979 HCAPLUS
DOCUMENT NUMBER: 140:373904
TITLE: TSK polypeptides, polynucleotides and antibodies for modulation of TGF-β-like signalling pathways and for wound healing, cancer therapy and drug screening
INVENTOR(S): Ohnuma, Shin-ichi; Lupo, Giuseppe; Harris, William; Ohta, Kunimasa; Kuriyama, Sei; Tanaka, Hideaki
PATENT ASSIGNEE(S): Cambridge University Technical Services Limited, UK; **Cancer Research Technology Limited**
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035627	A1	20040429	WO 2003-GB4535	20031021

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-24436 A 20021021

AB The present invention relates to the a new family of polypeptides which are extra-cellular modulators of members of the Transforming Growth Factor-β (TGF-β) superfamily, including TGFsss and BMPs, and are involved in embryogenesis and the pathogenesis of human disorders mediated by TGF-β superfamily signalling. These modulators are termed Tsukushi (TSK) polypeptides. Agents and methods for modulating (TGF-β)-like mol. signalling pathways using TSK polypeptides are provided. TSK proteins, polynucleotides and antibodies are useful for wound healing, tissue repair, bone and cartilage formation, cancer therapy and drug screening.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

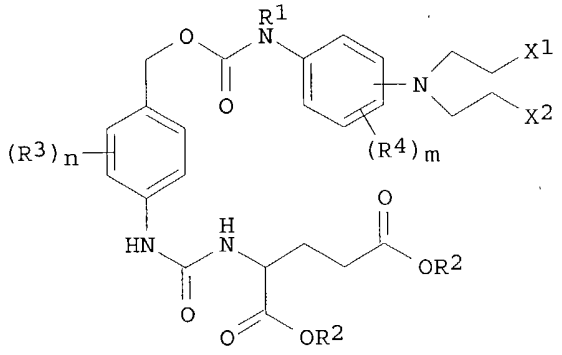
L36 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:203803 HCAPLUS
DOCUMENT NUMBER: 140:253908
TITLE: Preparation of ureidoglutamate-containing enzyme activated self-immolative N-substituted nitrogen mustard prodrugs
INVENTOR(S): Springer, Caroline Joy; Niculescu-Duvaz, Ion; Niculescu-Duvaz, Dan M.
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004020400	A1	20040311	WO 2003-GB3736	20030901

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,

GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: GB 2002-20319 A 20020902
OTHER SOURCE(S): MARPAT 140:253908
GI



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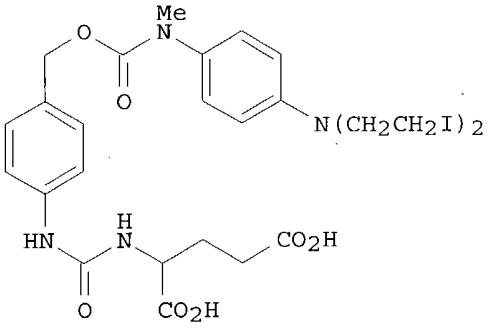

II

AB Title compds. (I; R1 = C1-7 alkyl; X1, X2 = iodo, Br, Cl; R2 = H, ester substituent; m, n = 0-4; R3 = Ph substituent; R4 = mustard substituent), were prepared Thus, title compound (II) (multistep preparation using diallyl L-glutamate tosylate given) showed IC50 = 1.5 μM in WiDr colon carcinoma cells engineered for stable expression of (stCPG2(Q)3).
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:78614 HCAPLUS
DOCUMENT NUMBER: 140:141429
TITLE: Crystal structure of G-quadruplex human DNA and its use in modeling of the interaction of molecular structures
INVENTOR(S): Neidle, Stephen; Parkinson, Gary N.; Lee, Michael Pak Ho
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004018483	A1	20040129	US 2003-405085	20030402
PRIORITY APPLN. INFO.:			GB 2002-7623 A	20020402

AB The present invention relates to a crystal structure of G-quadruplexes of human DNA and its use. The invention provides a crystal of an intramol. G-quadruplex structure having a hexagonal space group P6, and unit cell dimensions a = b = 56.7 and c = 42.1; $\alpha = \beta = 90°$, $\gamma = 120°$. The three dimensional atomic coordinates of crystals of intramol. and intermol. G-quadruplexes are provided. These structures may be used in a computer-based method for the anal. of the interaction of a mol. structure with a G-quadruplex.

L36 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41754 HCAPLUS
DOCUMENT NUMBER: 140:90319
TITLE: 5T4 antigen expression
INVENTOR(S): Ward, Christopher M.; Stern, Peter L.; Carroll, Miles W.
PATENT ASSIGNEE(S): Oxford Biomedica (UK) Limited, UK; **Cancer Research Technology Limited**
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005926	A2	20040115	WO 2003-GB2836	20030702
WO 2004005926	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	GB 2002-15287	A	20020702
	US 2003-434885	A	20030509

AB The present invention relates to methods for detecting the differentiation status of stem cells comprising detecting the expression of 5T4 antigen in said stem cells. The present invention also relates to methods for separating populations of undifferentiated or differentiated mammalian stem cells through detection of 5T4 expression.

L36 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:972259 HCAPLUS
DOCUMENT NUMBER: 140:3789
TITLE: Disease classification
INVENTOR(S): Young, Bryan Douglas; Debernardi, Silvana; Tomlinson, Simon Roy
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 111 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003102235	A2	20031211	WO 2003-GB2315	20030528
WO 2003102235	A3	20040617		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-385065P P 20020531

AB A method of assigning a patient having or suspected of having acute myeloid leukemia (AML) to a cytogenetically defined AML class, the method comprising providing a sample from the patient, using gene expression profiling to determine the expression level of at least one informative gene in the sample, and using the at least one determined expression level to assign the sample to an AML class. The invention also includes a method of assigning a patient having or suspected of having AML to an AML class, comprising providing a sample from the patient, determining the expression level of at least one informative gene selected from the genes listed in Table 1 or Table 2 or Table 3 in the sample, and using the at least one determined expression level to assign the sample to an AML class.

L36 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:971960 HCAPLUS
DOCUMENT NUMBER: 140:2533
TITLE: Substrate for holding an array of experimental samples
INVENTOR(S): Alazawi, William Omar Farook; Roberts, Ian
PATENT ASSIGNEE(S): **Cancer Research Technology Ltd, UK**
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101618	A1	20031211	WO 2003-GB2362	20030530

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,

NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-12720 A 20020531
GB 2002-14789 A 20020626
US 2003-439968P P 20030114

AB A substrate (1) for holding an array of exptl. samples, particularly biol. samples, is provided. The substrate has a plurality of wells for holding resp. exptl. samples, wherein the bottom of each well is at one of a plurality of levels. The bottoms of nearest neighbor wells are at different levels, and there may several different levels of well bottoms across the entire substrate. Interference between samples in nearest-neighbor wells can be reduced or eliminated. Both high and low d. arrays of wells can be provided. Uses of the substrate include expression anal., proteomics, metabolome screening, antigen testing, SNP anal., microELISA, toxicity testing or live cell array anal. The size and configuration of the substrate (1) can be chosen depending on the desired application.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:875388 HCAPLUS
DOCUMENT NUMBER: 139:360689
TITLE: Inhibition of licensing of DNA replication complexes in transformed cells by geminin for screening drug
INVENTOR(S): Shreeram, Sathyavageeswaran; Blow, John Julian
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091385	A2	20031106	WO 2003-GB1804	20030425
WO 2003091385	A3	20040422		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-9508 A 20020425

AB The invention is based on the finding that the presence of the protein geminin in the G1 phase in transformed cells leads to a reduction in the number of licensed replication complexes but does not prevent the DNA of the attempting to replicate by entering S phase, resulting in a proportion of the cells undergoing apoptosis. This is in contrast to untransformed cells, where the lack of sufficient replication complexes will prevent the entry of the cells into S phase. The differential effect of geminin provides a basis for a cell based assay for drug discovery, comprising: providing a candidate compound; providing a sample of transformed and a sample of untransformed cells; and determining whether said compound is capable of

reducing the number of licensed replication origins in said cells present in the G1 phase. Geminin expression significantly abolished the colony forming ability of cell line U20S and Saos2 compared to controls. Geminin inhibited the DNA replication by inhibition of Cdt1. Ad5GFP-geminin infection caused a strong reduction of chromatin-bound Mcm2. Geminin expressing cells showed a marked sub-G1 population, consistent with geminin expression inducing apoptosis. Geminin-expressing U20S cells contained high levels of cyclin E, consistent with an S phase arrest. In contrast, cyclin A levels were low. Geminin-expressing cell containing high level of P53 and cip1/Waf1. As a consequence of forced geminin expression, U20S cells enter, but cannot complete, S phase. The inability to complete S phase triggers checkpoint pathways that lead to the down-regulation of cyclin A, the induction of Cip1/Waf1 and the induction of apoptosis.

L36 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:796749 HCAPLUS
DOCUMENT NUMBER: 139:306545
TITLE: Chemokines ESkine and PESKY and uses thereof in therapy
INVENTOR(S): Graham, Gerry
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082920	A1	20031009	WO 2003-GB1472	20030402

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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PRIORITY APPLN. INFO.: GB 2002-7624 A 20020402

AB The disclosed invention concerns a nuclear targeting signal found in the C-terminal sequence of constitutive chemokines. The title chemokines have a nuclear targeting domain in their C-terminal sequence which provides the ability of the polypeptide to translocate to the cell nucleus in a receptor-independent fashion; this nuclear targeting can also take place following receptor-mediated internalization. The invention provides nuclear targeting polypeptides (NTP) isolated from chemokines and complexes comprising either the intact chemokine or just the nuclear targeting domain and substances to be transported to the cell nucleus. The nuclear translocation of ESkine variant PESKY is associated with cytoskeletal rearrangements involving alterations in the cellular actin cytoskeleton and leading to enhanced motility of PESKY-expressing cells. These NTP can be used in the preparation of therapeutics for treating cancer.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:776826 HCAPLUS
DOCUMENT NUMBER: 139:271036
TITLE: Anticancer combinations of xanthenone-type compounds and NSAIDs
INVENTOR(S): Wang, Liang-chuan Steve; Paxton, James William; Ching, Lai-ming; Baguley, Bruce Charles; Kestell, Philip
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: Brit. UK Pat. Appl., 31 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2386836	A1	20031001	GB 2002-6839	20020322
WO 2003080044	A1	20031002	WO 2003-GB1320	20030320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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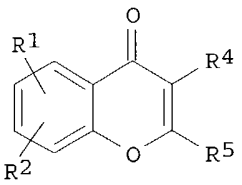
PRIORITY APPLN. INFO.: GB 2002-6839 A 20020322
OTHER SOURCE(S): MARPAT 139:271036
GI



I

AB Method of modulating neoplastic growth comprises synergistically administering to a mammal, including humans, (i) a compound of formula I [(a) R1-3 = H, C1-6 alkyl, halo, CF3, CN, NO2, NH2, OH, OR, NHCOR, NHSO2R, SR, SO2R, NHR; R = C1-6 alkyl or alkoxy; R4-5 = 6-membered aromatic ring substituted by R3 and (B)-CO2H, (B) = linear/branched (un)substituted (ethylenically un)saturated C1-6 alkyl; (b) R1 = H, C1-6 alkyl or alkoxy; R2 = (B)-CO2H; R4-5 = H, Ph, C1-6 alkyl, cycloalkyl, thenyl, furyl, naphthyl, aralkyl; R2 = (B)-CO2H], including DMXAA, or its salt or ester, and (ii) either concomitantly or sequentially administering a non-steroidal anti-inflammatory drug (NSAID), e.g. diclofenac, salicylate, ibuprofen, celecoxib or rofecoxib, at an amount less than that required to substantially alter the plasma pharmacokinetics of compound I in the mammal. For example, coadministration of diclofenac (5 mg/kg) with DMXAA (25 mg/kg) led to an improved antitumor activity in colon 38 tumor-bearing mice. Diclofenac alone had no effect on the growth of colon 38 tumors,

DMXAA alone produced a growth delay of about 6 days, but none of the mice were cured, while the combination showed 100% cure.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:719311 HCAPLUS
DOCUMENT NUMBER: 139:257718
TITLE: Materials and methods relating to the treatment of lymphoma
INVENTOR(S): Zhu, Delin; Stevenson, Freda
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074059	A2	20030912	WO 2003-GB783	20030224
WO 2003074059	A3	20040108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-5395 A 20020307
AB The invention provides materials and methods for diagnosing and treating non-Hodgkins lymphoma, particularly follicular lymphoma and Burkitt's lymphoma, based on the abnormal glycosylation status of the Igs on B lymphocytes.

L36 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:634074 HCAPLUS
DOCUMENT NUMBER: 139:175556
TITLE: Sequences of heat shock protein 90 activator Aha1 and therapeutic use
INVENTOR(S): Workman, Paul; Aherne, Wynne; Pearl, Laurence; Prodromou, Chrisostomos
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003067262	A2	20030814	WO 2003-GB492	20030204
WO 2003067262	A3	20040108		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-2871 A 20020207

AB This invention relates the identification of a novel co-factor (termed 'Aha1') that interacts with the mol. chaperone Heat shock protein 90 (Hsp90) and stimulates Hsp90 activity. Various assay methods and therapeutic applications based on this interaction are provided.

L36 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:570961 HCAPLUS

DOCUMENT NUMBER: 139:133476

TITLE: Preparation of acridone and acridine compounds as telomerase inhibitors for use in pharmaceutical compns. for the treatment of cancer and other proliferative diseases

INVENTOR(S): Neidle, Stephen; Harrison, Richard John; Kelland, Lloyd Royston; Gowan, Sharon Michele; Read, Martin Anthony; Reszka, Anthony

PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**

SOURCE: PCT Int. Appl., 144 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059885	A1	20030724	WO 2003-GB102	20030114

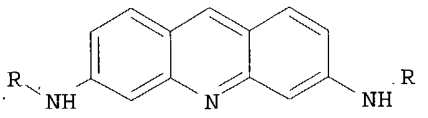
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-347899P P 20020115

OTHER SOURCE(S): MARPAT 139:133476

GI



I

AB Acridones and acridines, such as I [R = alkyl, alkenyl, aminoalkyl, N-bound-heterocyclylalkyl, alkoxyalkyl, etc.], were prepared for therapeutic use in the treatment of cancer and other proliferative conditions. Thus, BSU-SB-36/102 I (R = CH2CH:CH2) was prepared in quant. yield by reaction of allyl bromide with the corresponding di-BOC-protected-acridinediamine I (R = CO2CMe3). Hydrochloride salts of the prepared acridines were tested for telomerase inhibitory activity and for growth inhibition of human ovarian carcinoma cell lines A2780, CH1 and SKOV-3.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:532767 HCAPLUS
DOCUMENT NUMBER: 139:96312
TITLE: A system for stable expression of siRNAs targeted to RNA polymerase III specific genes in mammalian cells applicable in gene therapy
INVENTOR(S): Agami, Reuven; Brummelkamp, Thijn
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003056012	A1	20030710	WO 2002-GB5802	20021219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
GB 2383330	A1	20030625	GB 2002-18556	20020809
US 2003144232	A1	20030731	US 2002-216054	20020809
EP 1458863	A1	20040922	EP 2002-788185	20021219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:

GB 2001-30955	A	20011224
US 2002-377482P	P	20020502
GB 2002-18556	A	20020809
US 2002-216054	A	20020809
WO 2002-GB5802	W	20021219

AB The present invention provides a polynucleotide comprising a RNA polymerase III promoter, a region encoding a siRNA, and a transcriptional termination element comprising five consecutive thymine residues. Specifically, siRNAs designed to target promoters of genes for H1 RNA, or CdH1, or p53 or CDC20, K-RASV12 (V12 mutant allele) are provided. Addnl. targets can include gene promoters for RNA polymerase III 5S, U6, adenovirus VA1, Vault, telomerase RNA, or tRNA. In general, the region encoding the siRNA comprises: a region complementary to a target gene and a second region complementary to the first region; and a spacer with the sequence 5'TTCAAGAGA3' separating the two complementary regions. The stem loop

structure formed by siRNA can be cleaved by an enzyme to generate a siRNA mol. which 3' overhangs at each of its termini each comprising two uridine residues. The invention also provides for vectors, cells and non-human transgenic animal comprising the polynucleotides of the invention as well as their use in medicaments for various conditions.

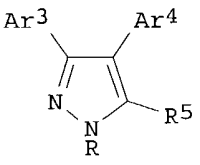
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:532647 HCAPLUS
DOCUMENT NUMBER: 139:101122
TITLE: Preparation of 3,4-diarylpyrazoles as inhibitors of heat shock protein 90 (HSP90) and their use in the therapy of cancer
INVENTOR(S): Drysdale, Martin James; Dymock, Brian William; Barril-Alonso, Xavier; Workman, Paul; Pearl, Laurence Harris; Prodromou, Chrisostomos; MacDonald, Edward
PATENT ASSIGNEE(S): Ribotargets Limited, UK; **Cancer Research Technology Limited**; The Institute of Cancer Research
SOURCE: PCT Int. Appl., 299 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055860	A1	20030710	WO 2002-GB5778	20021219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1456180	A1	20040915	EP 2002-805823	20021219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: GB 2001-30733 A 20011221
GB 2002-25688 A 20021104
WO 2002-GB5778 W 20021219

OTHER SOURCE(S): MARPAT 139:101122
GI



I

AB A method of inhibiting HSP90 comprises administration of title compds. [I; Ar3, Ar4 = (substituted) C5-20 aryl; R5 = H, halo, OH, ether, formyl, acyl, CO2H, ester, acyloxy, oxycarbonyloxy, amido, acylamido, aminocarbonyloxy, tetrazolyl, amino, NO2, cyano, N3, sulfhydryl, thioether, sulfonamido, C1-7 alkyl, C3-20 heterocyclyl, C5-20 aryl; R = H, C1-7 alkyl, C3-20 heterocyclyl, C5-20 aryl] and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemical protected forms, and prodrugs thereof. Thus, 7-hydroxy-3-phenylchromen-4-one and hydrazine hydrate were refluxed 45 min. in EtOH to give 4-(4-phenyl-1H-pyrazol-3-yl)benzene-1,3-diol. This inhibited HSP90 activity with IC50 = 10-100 μM.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:491394 HCAPLUS
DOCUMENT NUMBER: 139:32912
TITLE: Materials and methods relating to the production and maintenance of cell lines
INVENTOR(S): Spits, Hergen; Naspetti, Marianne; Scheeren, Ferenc; Blom, Bianca
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003052083	A2	20030626	WO 2002-GB5753	20021218
WO 2003052083	A3	20031127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1458855	A2	20040922	EP 2002-788154	20021218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:

GB 2001-30223	A	20011218
GB 2002-6086	A	20020314
WO 2002-GB5753	W	20021218

AB The invention provides methods for maintaining cell lines from primary cells, i.e. non-transformed cells, using expression of the signal transducer of activation and transcription (STAT). The methods are particularly suitable for the maintenance of B-cells.

L36 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:301218 HCAPLUS
DOCUMENT NUMBER: 138:315846
TITLE: Reporter constructs comprising cell cycle phase-specific control element and destruction control

element for determining cell cycle position
INVENTOR(S): Pines, Jonathon Noe; Thomas, Nicholas; Jones, Anne Elizabeth; Goodyer, Ian David; Francis, Michael John; Ismail, Rahman Aziz; Kendall, Jonathan Mark
PATENT ASSIGNEE(S): Amersham Biosciences UK Limited, UK; **Cancer Research Technology Limited**
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031612	A2	20030417	WO 2002-GB4258	20020912
WO 2003031612	A3	20031030		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1432819	A2	20040630	EP 2002-760417	20020912
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: GB 2001-23856 A 20011005
WO 2002-GB4258 W 20020912

AB The invention provides a novel, non-destructive and dynamic process for determining the cell cycle position of living cells. The invention also provides DNA constructs, and cell lines containing such constructs, that exhibit activation and deactivation of a detectable reporter mol. in a cell cycle specific manner. The invention thus allows greater precision in determining cell cycle phase status than existing techniques and further provides a method for continuous monitoring of cell cycle progression in individual cells.

L36 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:282509 HCAPLUS
DOCUMENT NUMBER: 138:304053
TITLE: Preparation of 4-(alkoxy)-substituted chalcones as antiproliferative agents
INVENTOR(S): Potter, Gerard Andrew; Ijaz, Taeeba
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029176	A1	20030410	WO 2002-GB4462	20020930
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

EP 1432669 A1 20040630 EP 2002-762611 20020930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: GB 2001-23780 A 20011003
WO 2002-GB4462 W 20020930

OTHER SOURCE(S): MARPAT 138:304053

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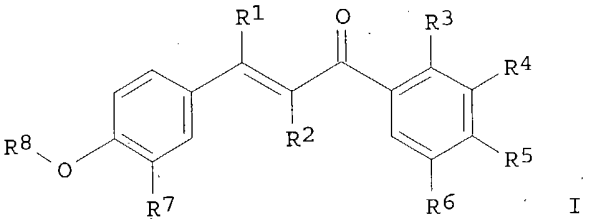


I

AB Title compds. I [R1-2 = H, alkyl, aryl; R3-6 = H, OH, MeO; R7 = H, OH, OCOR9, OSO2R9, etc.; R8 = alkyl; R9 = alkyl, heterocyclyl, aryl] are prepared For instance, 4-ethoxybenzaldehyde was condensed with 3,5-dimethoxyacetophenone (MeOH, NaOH, 2 h) to give (E)-1-(4-ethoxyphenyl)-3-(3,5-dimethoxyphenyl)prop-1-en-3-one as yellow crystals. Selected example compds. show tumor selective cytotoxicity activity in an MCF-7 cell line assay. I are useful in vitro and in vivo for diagnosis and treatment of, e.g., proliferative conditions, such as cancer, and inflammatory conditions.

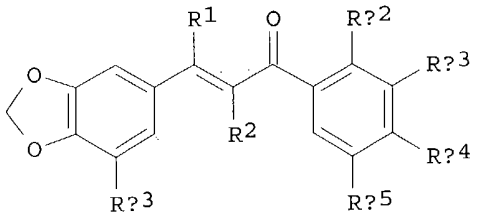
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:282385 HCAPLUS
DOCUMENT NUMBER: 138:297623
TITLE: Synthesis of 3,4-methylenedioxy-substituted chalcones as therapeutic agents for diagnosis and treatment of proliferative conditions
INVENTOR(S): Potter, Gerard Andrew; Butler, Paul Crispin
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003028713	A2	20030410	WO 2002-GB4406	20020930

WO 2003028713 A3 20030724
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1432413 A2 20040630 EP 2002-767671 20020930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
PRIORITY APPLN. INFO.: GB 2001-23777 A 20011003
WO 2002-GB4406 W 20020930

OTHER SOURCE(S): MARPAT 138:297623
GI



I

AB The present invention pertains to the use of a compound for the manufacture of a medicament for use in the treatment of a proliferative condition, wherein the compds. have the following formula (I): wherein: each of RB2, RB3, RB4, and RB5 is independently -H, -OH, or -OMe; each of R1 and R2 is independently: -H, optionally substituted C1-4 alkyl, or optionally substituted C5-20 aryl; RA3 is -H, -OH, -OC(=O)RE, -OS(=O)2OH, or -OP(=O)(OH)2; RE is: -H, optionally substituted C1-6 alkyl, optionally substituted C3-20 heterocyclyl, or optionally substituted C5-20 aryl; or a pharmaceutically acceptable salt, solvate, amide, ester, ether, chemical protected form, or prodrug thereof. The present invention also pertains to such compds., pharmaceutical compns. comprising such compds., and the use of such compds. and compns., both in vitro and in vivo, for both diagnosis and treatment of, for example, proliferative conditions, such as cancer, and inflammatory conditions.

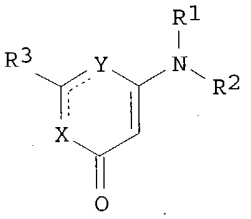
L36 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:242317 HCAPLUS
DOCUMENT NUMBER: 138:271533
TITLE: Preparation of aminopyranone and aminopyrimidinones as selective inhibitors of DNA-dependent protein kinase
INVENTOR(S): Griffin, Roger John; Golding, Bernard Thomas; Newell, David Richard; Calvert, Hilary Alan; Curtin, Nicola Jane; Hardcastle, Ian Robert; Martin, Niall Morrison Barr; Smith, Graeme Cameron Murray; Rigoreau, Laurent Jean Martin; Cockcroft, Xiao-Ling Fan; Loh, Vincent Ming-Lai, Jr.; Workman, Paul; Raynaud, Florence Irene; Nutley, Bernard Paul

PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 178 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024949	A1	20030327	WO 2002-GB3781	20020814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
GB 2393653	A1	20040407	GB 2004-1411	20020814
EP 1417196	A1	20040512	EP 2002-751439	20020814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004192687	A1	20040930	US 2004-486816	20040213
PRIORITY APPLN. INFO.:			GB 2001-19865	A 20010814
			WO 2002-GB3781	W 20020814

OTHER SOURCE(S): MARPAT 138:271533
GI



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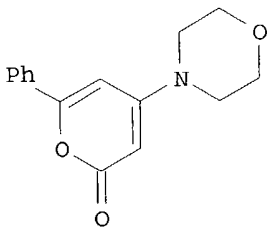

II

AB The invention relates to the use of heterocyclic compds. I [R1, R2 = H, (un)substituted C1-7 alkyl, C3-20 heterocyclyl, C5-20 aryl, or NR1R2 = (un)substituted 4-8 membered heterocyclic ring; X, Y = CR4 and O, O and CR'4, NR'4 and N where the unsatn. is in the appropriate place in the ring, and where 1 of R3 and R4 or R'4 = (un)substituted C3-20 heteroaryl or C5-20 aryl,and the other of R3 and R4 or R'4 = H; or R3 and R4 or R'4 together = -A-B-, which collectively represent a fused (un)substituted aromatic ring] and isomers, salts, solvates, chemical protected forms, and prodrugs thereof, in the preparation of a medicament for inhibiting the activity of DNA-dependent protein kinase (DNA-PK). The compds. also selectively inhibit the activity of DNA-PK compared to PI 3-kinase and/or ataxia-telangiectasia mutated (ATM) protein. Thus, condensation of acetophenone with CS2, followed by S-alkylation, substitution with morpholine, further S-alkylation, and cyclocondensation with Et bromoacetate, gave morpholine-substituted pyranone II. II inhibited DNA-PK with IC50 = 1.0 μM.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202462 HCAPLUS
DOCUMENT NUMBER: 138:226761
TITLE: Synergistic anticancer combinations containing 5,6-dimethylxanthenone-4-acetic acid
INVENTOR(S): Wilson, William Robert; Siim, Bronwyn Gae
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020259	A2	20030313	WO 2002-GB4025	20020903
WO 2003020259	A3	20030417		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1423105	A2	20040602	EP 2002-758562	20020903
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: GB 2001-21285 A 20010903
WO 2002-GB4025 W 20020903

AB The present invention relates to synergistic combinations of the 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and a compound selected from platinum compds., Vinca alkaloids, alkylating agents, anthracyclines, topoisomerase I inhibitors, antimetabolites and topoisomerase II inhibitors, which have antitumor activity. More particularly, the invention is concerned with the use of such combinations in the treatment of cancer and pharmaceutical compds. containing the combinations. The antitumor activity and host toxicity of DMXAA/cytotoxic drug combinations was assessed by varying the dose of chemotherapeutic drug up to the toxicity limit, with co-administration of a fixed DMXAA dose (80 μmol/kg, ca. 80% of MTD), and evaluating subsequent tumor growth delay. Of the 7 drugs investigated, 4 (doxorubicin, 5-fluorouracil, cyclophosphamide and cisplatin) had appreciable activity against this tumor as indicated by dose-response relationships providing significant slopes by linear regression, and highly significant growth delays of 10 days at their MTDs.

L36 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:154255 HCAPLUS
DOCUMENT NUMBER: 138:205066
TITLE: Preparation of 2-morpholinothiopyran-4-ones as DNA protein kinase inhibitors
INVENTOR(S): Griffin, Roger John; Golding, Bernard Thomas; Newell, David Richard; Calvert, Hilary Alan; Curtin, Nicola

Jane; Hardcastle, Ian Robert; Martin, Niall Morrison Barr; Smith, Graeme Cameron Murray; Rigoreau, Laurent Jean Martin; Workman, Paul; Raynaud, Florence Irene; Nutley, Bernard Paul

PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015790	A1	20030227	WO 2002-GB3740	20020814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1416936	A1	20040512	EP 2002-751427	20020814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: GB 2001-19863 A 20010814
WO 2002-GB3740 W 20020814

OTHER SOURCE(S): MARPAT 138:205066
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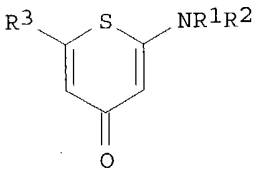

I

AB Title compds. [I; R1, R2 = H, (substituted) alkyl, heterocyclyl, aryl; NR1R2 = (substituted) heterocyclyl; R3 = (substituted) heterocyclyl, aryl], were prepared Thus, 2-morpholin-4-yl-6-phenylthiopyran-4-one (preparation outlined) inhibited DNA-PK with IC50 = 0.6 μM.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 30 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:76979 HCAPLUS
DOCUMENT NUMBER: 138:147699
TITLE: High-throughput screening for DNA-modifying enzyme inhibitors for use as anti-tumor agents
INVENTOR(S): Hammonds, Timothy Robin

PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003008643	A2	20030130	WO 2002-GB3345	20020722
WO 2003008643	A3	20030821		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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PRIORITY APPLN. INFO.: US 2001-306824P P 20010720

AB The present invention provides a polynucleotide having a double stranded portion which is interrupted by at least one residue of the polynucleotide which does not participate in an A-T or G-C base pair, the mol. further having attached thereto a fluorescent moiety and a quenching moiety which quenches the fluorescence of the fluorescent moiety. The invention further provides assays and methods using said polynucleotides for detecting activity of DNA modifying enzymes whose recognition sites commonly features residues that do not participate in Watson-Crick base pairing. These methods may be used for high-throughput drug screening for anti-tumor agents.

L36 ANSWER 31 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:76617 HCAPLUS
DOCUMENT NUMBER: 138:131087
TITLE: New use
INVENTOR(S): Hickson, Ian david; Hammonds, Timothy Robin
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 150 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007955	A2	20030130	WO 2002-GB3342	20020722
WO 2003007955	A3	20030501		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,

NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-306679P P 20010720
OTHER SOURCE(S): MARPAT 138:131087
AB The present invention provides the use of a low mol. weight mammalian AP endonuclease inhibitor for the preparation of a medicament for the treatment of cancer. Markushes included.

L36 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:42257 HCAPLUS
DOCUMENT NUMBER: 138:106698
TITLE: Preparation of 4-arylquinols and analogs thereof as antiproliferative agents, anticancer agents, antimycobacterial agents, antituberculosis agents, and/or thioredoxin/thioredoxin reductase inhibitors
INVENTOR(S): Stevens, Malcolm Francis Graham; Wells, Geoffrey; Westwell, Andrew David; Poole, Tracey Dawn
PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**
SOURCE: PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004479	A1	20030116	WO 2002-GB3097	20020705
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1404659	A1	20040407	EP 2002-745585	20020705
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PRIORITY APPLN. INFO.: GB 2001-16594 A 20010706
WO 2002-GB3097 W 20020705

OTHER SOURCE(S): MARPAT 138:106698
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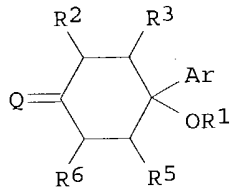

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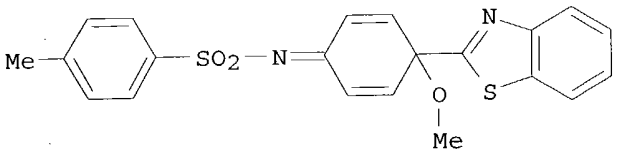

II

AB The present invention pertains to compds. of the formula (I) (wherein: Q is O or :NSO2R; R is H or optionally substituted C1-7 alkyl, C3-20 heterocyclyl, or C5-20 aryl; Ar is optionally substituted C5-20 aryl; R1 is H or an oxy substituent such as optionally substituted C1-7 alkyl, C3-20 heterocyclyl, C5-20 heterocyclyl, C5-20 aryl, C1-7 alkylacyl, C3-20 heterocyclyl-acyl, or C5-20 aryl-acyl; the bond marked α is a single bond or a double bond; the bond marked β is a single bond or a double bond; R3 and R5 are each independently ring substituents; R2 and R6 are each independently ring substituents) and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof. The present invention also pertains to pharmaceutical compns. comprising the compds. I, and the use of the compds. I and compns., both in vitro and in vivo, for example, in the treatment of proliferative conditions, (e.g., cancer), mycobacterial infections (e.g., tuberculosis), and/or conditions mediated by thioredoxin/thioredoxin reductase. These compds. I are useful as antiproliferative agents, anticancer agents, antimycobacterial agents, antituberculosis agents, and/or thioredoxin/thioredoxin reductase inhibitors (no data). Thus, to 0.5 g 2-(4-aminophenyl)benzothiazole in 6 mL pyridine was added 0.506 g p-toluenesulfonyl chloride in 4 mL pyridine, heated at reflux for 10 min, cooled, and treated with 10 mL water to 96% N-[(4-benzothiazol-2-yl)phenyl]-4-methylbenzenesulfonamide which (0.1 g) was dissolved in 2 mL MeOH and stirred with BTIB (1.1 15 equivalent) at room temperature for 5 h to give 73% N-[4-methoxy-4-(benzothiazol-2-yl)cyclohexa-2,5-dienylidene]-4-methylbenzenesulfonamide (II). 4-(Benzothiazol-2-yl)-4-hydroxy-2,5-cyclohexandien-1-one in vitro showed IC50 of 0.04, 0.38, 0.35, 0.79, and 2.35 μM for inhibiting the proliferation of HCT and HT29 human colon carcinoma, human MCF-7 and MDA 468 breast carcinoma, and A549 human lung adenocarcinoma, resp.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:522544 HCAPLUS

DOCUMENT NUMBER: 137:83618

TITLE: Modifided carboxypeptidase G2 enzymes for antitumor use

INVENTOR(S): Begent, Richard H. J.; Chester, Kerry; Minton, Nigel P.; Rees, Anthony R.; Sharma, Surinder K.; Spencer, Daniel I. R.

PATENT ASSIGNEE(S): **Cancer Research Technology Limited, UK**

SOURCE: U.S. Pat. Appl. Publ., 23 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002090709	A1	20020711	US 2001-898461	20010705
US 6656718	B2	20031202		
PRIORITY APPLN. INFO.:			US 2000-216689P P	20000707

AB The invention relates to improvements relating to cancer therapy based on the identification of a number of regions of CPG2 which contain epitopes which appear to be involved in the production of a host immune response and which may be modified to alter the immunogenicity in patients. Production of fusions of CPG2 with an antibody, where the CPG2 protein has been tagged provides a CPG2 protein which has reduced immunogenicity. By using partially glycosylated enzyme obtainable by P. pastoris expression, the efficacy of antibody-CPG2 fusions is enhanced.

L36 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:332370 HCAPLUS
DOCUMENT NUMBER: 136:351365
TITLE: Methods relating to nucleic acid amplification and methylation profiling by fluorescence melting curve analysis
INVENTOR(S): Guldberg, Per
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK; **Cancer Research Technology Ltd.**
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034942	A2	20020502	WO 2001-GB4707	20011023
WO 2002034942	A3	20030605		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002010700	A5	20020506	AU 2002-10700	20011023
EP 1334209	A2	20030813	EP 2001-978601	20011023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004512050	T2	20040422	JP 2002-537911	20011023
US 2004048275	A1	20040311	US 2003-399899	20031003
PRIORITY APPLN. INFO.:			GB 2000-25913 A	20001023
			GB 2001-7547 A	20010326
			WO 2001-GB4707 W	20011023

AB The invention provides improved methods for determining the methylation profile of a nucleic acid sequence and for determining one or more base changes in the

target nucleic acid sequence as compared to a corresponding control sequence. The methods are one-step methods which can be incorporated with known amplification techniques such as PCR. The invention also provides methods for determining changes in nucleic acid sequences either via their methylation profile or owing to mutations of one or more bases. The inventors have shown that fluorescence melting curve anal. is a fast and cost-effective method that can be fully integrated with PCR for detection of aberrant DNA methylation patterns. Once the bisulfite conversion of sample DNA has been performed, screening of samples can be completed in less than 45 min by using standard PCR reagents. One of the strongest features of the present method is that it can resolve heterogeneous methylation patterns.

L36 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90013 HCAPLUS
DOCUMENT NUMBER: 136:134683
TITLE: Preparation of bis(aminoalkanamido)acridine-9-amines and analogs as telomerase inhibitors
INVENTOR(S): Neidle, Stephen; Harrison, Richard john; Kelland, Lloyd Royston; Gowan, Sharon Michele; Read, Martin; Reszka, Tony
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK; **Cancer Research Technology Limited**
SOURCE: PCT Int. Appl., 171 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002008193	A2	20020131	WO 2001-GB3046		20010706
WO 2002008193	A3	20031002			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1363888	A2	20031126	EP 2001-947645		20010706
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
JP 2004510706	T2	20040408	JP 2002-514100		20010706
US 2003207909	A1	20031106	US 2003-332261		20030404
PRIORITY APPLN. INFO.:			US 2000-216624P	P	20000707
			WO 2001-GB3046	W	20010706

OTHER SOURCE(S): MARPAT 136:134683
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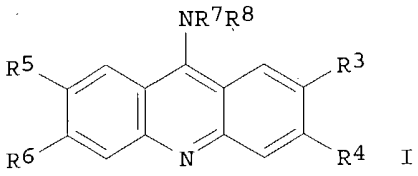

I

AB Title compds. [e.g., I; 2 of R3 or R4 and R5 or R6 = NHCO(CH2)nNR1R2 and the others = H; R1,R2,R7 = H, alkyl, heterocyclyl, aryl; NR1R2 = heterocyclyl; R8 = (un)substituted alkyl, -heterocyclyl, -aryl; n = 1-5] were prepared Thus, 3,6-bis(3-pyrrolidinopropionamido)-9(10H)-acridinone (preparation given) was treated with POCl3 and the product aminated by 4-(Me2N)C6H4NH2 to give I [R3 = R5 = R7 = H, R4 = R6 = NHCOCH2CH2R, R = pyrrolidino, R8 = C6H4(NMe2)-4]. Data for biol. activity of title compds. were given.

L36 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:449153 HCAPLUS
DOCUMENT NUMBER: 115:49153
TITLE: Preparation of 2,6-bis(aminoalkanoylamino)anthracene-9,10-diones as intercalating agents
INVENTOR(S): Neidle, Stephen; Jenkins, Terence Charles; Agbandje, Mavis
PATENT ASSIGNEE(S): **Cancer Research Technology Ltd., UK**
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9100265	A1	19910110	WO 1990-GB1004	19900629
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
EP 482119	A1	19920429	EP 1990-917804	19900629
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
PRIORITY APPLN. INFO.:			GB 1989-15028	19890630
			WO 1990-GB1004	19900629

OTHER SOURCE(S): MARPAT 115:49153
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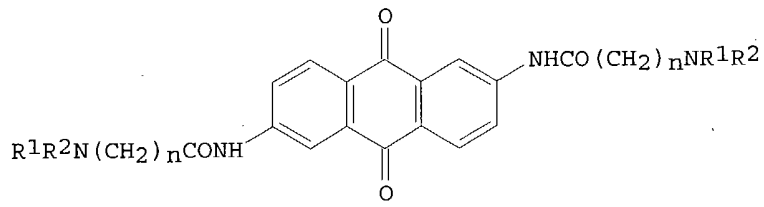

I

AB The title compds. [I; n = 1, 2, 3; R1, R2 = Et, CH2CH2OH, CH2OH; or R1R2N = piperidino, 2- or 4-(2-hydroxyethyl)piperidino, 2-(hydroxymethyl)piperidino, 4-(2-hydroxyethyl)- or 4-methylpiperidino,

morpholino], useful for treating a host suffering from cancer, are prepared I intercalating into DNA with one side-chain of the mol. residing in each DNA groove, are cytotoxic and non-mutagenic. Thus, a suspension of 14.3 mmol 2,6-bis(3-chloropropionamido)anthracene-9,10-dione in EtOH was gently refluxed and 0.12 mol 4-(2-hydroxyethyl)piperidine in EtOH was added dropwise during 30 min and refluxing was continued for 5 h to give I [n = 2, R1R2N = 4-(2-hydroxyethyl)piperidino] (II). I stabilized various DNA's towards thermal denaturation, the effect of increasing the melting temperature for the DNA by I (n = 2) was comparable to that of mitoxantrone (III) (a known intercalator), and unwinded covalently-colored supercoiled plasmid PM2 DNA. I in vitro showed IC50 of 0.25 - >100 μmol/dm3 against L1210 leukemia cell lines, vs. 0.002 μmol/dm3 with III. II.2AcOH at 200 mg/kg/day i.p. on days 3, 5, 6, and 7 increased 136.8% the life span of mice bearing L1210 leukemia tumor.

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=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 14:57:42 ON 05 OCT 2004
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FILE COVERS 1907 - 5 Oct 2004  VOL 141 ISS 15
FILE LAST UPDATED: 4 Oct 2004  (20041004/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l17
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DMXAA/CN
L7           121 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L8        186425 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+OLD,NT/CT
L9           106 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND L8
L10          842 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "COMBINATION CHEMOTHERAPY"/CT

L11      1251578 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 OR ?COMBI?/BI
L12           38 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND L11
L17            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND (P/DT AND (PY<=2001
                  OR PRY<=2001 OR AY<=2001))


=> b medl
FILE 'MEDLINE' ENTERED AT 14:59:13 ON 05 OCT 2004

 FILE LAST UPDATED: 2 OCT 2004 (20041002/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l34
L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DMXAA/CN
L20          526 SEA FILE=MEDLINE ABB=ON  PLU=ON  XANTHONES/CT OR DMXAA OR
                  ?DIMETHYLXANTHENONE?/BI
L21        86699 SEA FILE=MEDLINE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENTS"/CT
L24        35788 SEA FILE=MEDLINE ABB=ON  PLU=ON  L21(L)TU
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L25          29 SEA FILE=MEDLINE ABB=ON  PLU=ON  L24 AND L20
L26         526 SEA FILE=MEDLINE ABB=ON  PLU=ON  L6 OR L20
L28          29 SEA FILE=MEDLINE ABB=ON  PLU=ON  L25 AND L26
L34           8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L28 AND COMBI?


=> b biosis
FILE 'BIOSIS' ENTERED AT 14:59:21 ON 05 OCT 2004
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 September 2004 (20040929/ED)

FILE RELOADED: 19 October 2003.

=> d que l33
L6            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DMXAA/CN
L29         129 SEA FILE=BIOSIS ABB=ON  PLU=ON  L6 OR DMXAA OR ?DIMETHYLXANTHEN
                ONE? OR ?DIMETHYL(A)XANTHENONE?
L30         208 SEA FILE=BIOSIS ABB=ON  PLU=ON  ?XANTHENON? OR L29
L31         172 SEA FILE=BIOSIS ABB=ON  PLU=ON  (?NEOPLAS? OR ?CANC? OR
                ?TUMOR? OR ?TUMOUR?) AND L30
L32         124 SEA FILE=BIOSIS ABB=ON  PLU=ON  L31 AND PY<=2001
L33          30 SEA FILE=BIOSIS ABB=ON  PLU=ON  COMBI? AND L32


=> dup rem l33 l34 l17
FILE 'BIOSIS' ENTERED AT 14:59:40 ON 05 OCT 2004
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FILE 'MEDLINE' ENTERED AT 14:59:40 ON 05 OCT 2004

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PROCESSING COMPLETED FOR L33
PROCESSING COMPLETED FOR L34
PROCESSING COMPLETED FOR L17
L35          42 DUP REM L33 L34 L17 (5 DUPLICATES REMOVED)

=> d ibib abs hitind l35 1-42

L35  ANSWER 1 OF 42  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:434278  HCAPLUS
DOCUMENT NUMBER:          139:921
TITLE:                    Combination bacteriolytic therapy for the
                          treatment of tumors
INVENTOR(S):              Dang, Long; Kinzler, Kenneth W.; Vogelstein, Bert
PATENT ASSIGNEE(S):       The Johns Hopkins University, USA
SOURCE:                   PCT Int. Appl., 33 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
```

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045153	A1	20030605	WO 2002-US37509	20021121 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1446012	A1	20040818	EP 2002-786766	20021121 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.:	US 2001-331786P	P	20011121 <--
	WO 2002-US37509	W	20021121

AB Current chemotherapeutic approaches for cancer are in part limited by the inability of drugs to destroy neoplastic cells within poorly vascularized compartments of tumors. We have here systematically assessed anaerobic bacteria for their capacity to grow expansively within avascular compartments of transplanted tumors. Among 26 different strains tested, one (Clostridium novyi) appeared particularly promising. We created a strain of C. novyi devoid of its lethal toxin (C. novyi-NT) and showed that i.v. injected C. novyi-NT spores germinated within the avascular regions of tumors in mice and destroyed surrounding viable tumor cells. When C. novyi-NT spores were administered together with conventional chemotherapeutic drugs, extensive hemorrhagic necrosis of tumors often developed within 24 h, resulting in significant and prolonged anti-tumor effects. This strategy, called **combination** bacteriolytic therapy (COBALT), has the potential to add a valuable dimension to the treatment of cancer.

IC ICM A01N063-00
ICS A01N065-00; A61K048-00; C12N001-12; C12N001-20; G01N033-53

CC 1-6 (Pharmacology)

ST cancer treatment **combination** bacteriolytic therapy Clostridium

IT Intestine, neoplasm
(colon, carcinoma; **combination** bacteriolytic therapy for treatment of tumors)

IT Intestine, neoplasm
(colorectal, metastasis; **combination** bacteriolytic therapy for treatment of tumors)

IT Anaerobic bacteria
Antitumor agents
Bacteriophage
Bifidobacterium longum
Clostridium novyi
Clostridium sordellii
Human
Hydration, physiological
Melanoma
Neoplasm
Radiotherapy
Spore
(**combination** bacteriolytic therapy for treatment of tumors)

IT Antibodies and Immunoglobulins
Steroids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(**combination** bacteriolytic therapy for treatment of tumors)
IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(damage, DNA-damaging agents; **combination** bacteriolytic therapy for treatment of tumors)
IT Drug delivery systems
(injections, i.v.; **combination** bacteriolytic therapy for treatment of tumors)
IT Drug delivery systems
(intratumoral; **combination** bacteriolytic therapy for treatment of tumors)
IT Toxins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(toxin-defective anaerobic bacterium; **combination** bacteriolytic therapy for treatment of tumors)
IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(toxin-encoding; **combination** bacteriolytic therapy for treatment of tumors)
IT Blood vessel
(tumor vasculature collapse; **combination** bacteriolytic therapy for treatment of tumors)
IT 50-07-7, Mitomycin C 50-18-0, Cytoxan 53-03-2, Prednisone 57-22-7, Vincristine 64-86-8, Colchicine 315-30-0, Allopurinol 865-21-4, Vinblastine 9002-12-4, Urate oxidase 110417-88-4, Dolastatin 10 117048-59-6, Combretastatin A-4 **117570-53-3**, 5,6-Dimethylxanthenone-4-acetic acid 143011-72-7, G-CSF
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**combination** bacteriolytic therapy for treatment of tumors)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 2 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202462 HCAPLUS
DOCUMENT NUMBER: 138:226761
TITLE: Synergistic anticancer **combinations** containing 5,6-dimethylxanthenone-4-acetic acid
INVENTOR(S): Wilson, William Robert; Siim, Bronwyn Gae
PATENT ASSIGNEE(S): Cancer Research Technology Limited, UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020259	A2	20030313	WO 2002-GB4025	20020903 <--
WO 2003020259	A3	20030417		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,

CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1423105 A2 20040602 EP 2002-758562 20020903 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: GB 2001-21285 A 20010903 <--

WO 2002-GB4025 W 20020903

AB The present invention relates to synergistic **combinations** of the 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and a compound selected from platinum compds., Vinca alkaloids, alkylating agents, anthracyclines, topoisomerase I inhibitors, antimetabolites and topoisomerase II inhibitors, which have antitumor activity. More particularly, the invention is concerned with the use of such **combinations** in the treatment of cancer and pharmaceutical compds. containing the **combinations.** The antitumor activity and host toxicity of DMXAA/cytotoxic drug **combinations** was assessed by varying the dose of chemotherapeutic drug up to the toxicity limit, with co-administration of a fixed DMXAA dose (80 μmol/kg, ca. 80% of MTD), and evaluating subsequent tumor growth delay. Of the 7 drugs investigated, 4 (doxorubicin, 5-fluorouracil, cyclophosphamide and cisplatin) had appreciable activity against this tumor as indicated by dose-response relationships providing significant slopes by linear regression, and highly significant growth delays of 10 days at their MTDs.

IC ICM A61K031-19

ICS A61K031-475; A61K031-505; A61K031-65; A61K031-66; A61K031-70; A61K033-24; A61P035-00; A61K031-19; A61K031-475; A61K031-505; A61K031-65; A61K031-66; A61K031-70; A61K033-24

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

ST synergistic anticancer **combination** dimethylxanthenoneacetic acid; xanthenoneacetic acid synergistic anticancer **combination**

IT Mammary gland, neoplasm

(carcinoma; synergistic anticancer **combinations**)

IT **Alkylating agents, biological**

Antitumor agents

Drug bioavailability

Human

(synergistic anticancer **combinations**)

IT Anthracyclines

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synergistic anticancer **combinations**)

IT **Antitumor agents**

(synergistic; synergistic anticancer **combinations**)

IT Alkaloids, biological studies

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(vinca; synergistic anticancer **combinations**)

IT 142805-56-9, Topoisomerase II 143180-75-0

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; synergistic anticancer **combinations**)

IT 50-18-0, Cyclophosphamide 51-21-8, 5-Fluorouracil 57-22-7, Vincristine 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 33419-42-0, Etoposide 41575-94-4, Carboplatin 95058-81-4, Gemcitabine 97682-44-5, Irinotecan

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synergistic anticancer **combinations**)

IT **117570-53-3**, 5,6-Dimethylxanthenone-4-acetic acid

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(synergistic anticancer **combinations** containing dimethylxanthenoneacetic acid)

L35 ANSWER 3 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511844 HCAPLUS
DOCUMENT NUMBER: 139:90457
TITLE: **Combined** compositions for tumor vasculature coaguligand treatment
INVENTOR(S): Thorpe, Philip E.; King, Steven W.; Gottstein, Claudia
PATENT ASSIGNEE(S): Board of Regents, The University of Texas System, USA
SOURCE: U.S. Pat. Appl. Publ., 98 pp.
CODEN: USXXCO
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003124132	A1	20030703	US 2002-259223	20020927 <--
WO 2003028840	A2	20030410	WO 2002-EP10913	20020927 <--
WO 2003028840	A3	20030828		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003129193	A1	20030710	US 2002-259227	20020927 <--
US 2003139374	A1	20030724	US 2002-259236	20020927 <--
US 2003211075	A1	20031113	US 2002-259244	20020927 <--
EP 1432447	A2	20040630	EP 2002-800138	20020927 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: US 2001-325532P P 20010927 <--
WO 2002-EP10913 W 20020927

AB Disclosed are various defined **combinations** of agents for use in improved antivascular therapies and coagulative tumor treatment. Particularly provided are **combined** treatment methods, and associated compns., pharmaceuticals, medicaments, kits and uses, which together function surprisingly effectively in the treatment of vascularized tumors. The invention preferably involves a component or treatment step that enhances the effectiveness of therapy using targeted or non-targeted coagulants to cause tumor vasculature thrombosis.

IC ICM A61K039-395
ICS A61K031-739
NCL 424178100; 514054000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 9, 15
IT **Angiogenesis inhibitors**
Antitumor agents
Blood coagulation
Coagulants
Human
Molecular cloning

Sarcoma
(compns. for tumor vasculature coaguligand treatment)
IT 50-35-1, Thalidomide 9001-25-6, Blood coagulation factor vii 9001-28-9, Blood coagulation factor ix 9001-29-0, Blood coagulation factor x 9002-05-5, Blood coagulation factor xa 9035-58-9, Blood-coagulation factor III 33419-42-0, Etoposide 37316-87-3, Blood coagulation factor ixa 53678-77-6, Muramyl dipeptide 57576-52-0, Thromboxane a2 60832-04-4, Thromboxane A2 synthase 78393-57-4, Blood coagulation factor II/Ia 82855-09-2, Combretastatin 83461-56-7, Mtppe 98982-74-2, Blood coagulation factor vii 105579-86-0, Threonyl-muramyl dipeptide 109971-63-3, Combretastatin A-1 109971-64-4, Combretastatin B-1 111394-44-6, Combretastatin A-2 111394-45-7, Combretastatin A-3 111394-46-8, Combretastatin B-2 116518-75-3, Combretastatin B-4 116518-76-4, Combretastatin B-3 117048-59-6, Combretastatin A-4 117048-60-9, Combretastatin A-5 117048-61-0, Combretastatin A-6 **117570-53-3**, DMXAA 117709-78-1, Combretastatin D-1 126191-23-9, Combretastatin D-2 138757-15-0, α2-Antiplasmin 157857-21-1, Maspin 188417-67-6, CM101
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for tumor vasculature coaguligand treatment)

L35 ANSWER 4 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:172911 HCAPLUS
DOCUMENT NUMBER: 138:198597
TITLE: Anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel
INVENTOR(S): Wilson, William Robert
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1287854	A1	20030305	EP 2001-307370	20010830 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			EP 2001-307370	20010830 <--

AB The present invention relates to synergistic **combinations** of the compound 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and taxanes, in particular paclitaxel and or docetaxel which have anti-tumor activity. More particularly, the invention is concerned with the use of such **combinations** in the treatment of cancer and pharmaceutical compns. containing said **combinations.**
IC ICM A61P035-00
ICS A61K031-35
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
IT Taxanes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel)
IT Drug delivery systems
(injections, i.v.; anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel)
IT **Antitumor agents**

(synergistic; anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel)

IT 114977-28-5, Docetaxel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel)

IT 33069-62-4, Paclitaxel **117570-53-3**, Dmxaa
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-cancer **combinations** of dmxaa and paclitaxel or docetaxel)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:107103 HCAPLUS
DOCUMENT NUMBER: 136:145217
TITLE: Xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment
INVENTOR(S): Baguley, Bruce Charles; Ching, Lai-Ming; Philpott, Martin
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009700	A1	20020207	WO 2001-NZ154	20010727 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1311262	A1	20030521	EP 2001-961455	20010727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004505047	T2	20040219	JP 2002-515253	20010727 <--
US 2004087611	A1	20040506	US 2003-341736	20030114 <--
PRIORITY APPLN. INFO.:			NZ 2000-506060 A	20000728 <--
			WO 2001-NZ154 W	20010727 <--

OTHER SOURCE(S): MARPAT 136:145217

AB The invention provides a method of treating cancer and compns. of use in such a method, the method including administering, either sequentially or simultaneously, (i) a compound of the xanthenone acetic acid group of compds., and (ii) at least one compound selected from compds. which modulate TNF production and compds. which act on biochem. pathways leading to TNF synthesis, the composition including a **combination** of (i) and (ii) above together with acceptable pharmaceutical carriers and/or vehicles.

IC ICM A61K031-352
ICS A61P035-00

CC 1-6 (Pharmacology)
Section cross-reference(s): 63

ST xanthenone acetic acid deriv TNF modulator antitumor **combination**

IT Ligands
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD14 receptor- binding; xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT Lipopolysaccharides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and deacylated LPS; xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to CD14 receptors; xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT **Antitumor agents**
Drug delivery systems
Drug interactions
Leukocyte
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT CD14 (antigen)
Receptors
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT Interleukin 1α
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT 141436-78-4, Protein kinase C 375798-61-1, Protein phosphatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT **117570-53-3**, 5,6-Dimethylxanthenone-4-acetic acid 129095-08-5, DMXAA sodium salt
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT 87626-55-9, Flavone acetic acid
RL: PAC (Pharmacological activity); BIOL (Biological study)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

IT 90-47-1D, Xanthenone, derivs. 16561-29-8, Phorbol myristate acetate 78111-17-8, Okadaic acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(xanthenone acetic acid compound-TNF modulator **combination** for cancer treatment)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 6 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:693118 HCAPLUS
DOCUMENT NUMBER: 137:195564
TITLE: Use of xanthenone-4-acetic acid in the manufacture of a medicament in the treatment of hyperproliferative

disorders
INVENTOR(S): Bellnier, David A.; Dougherty, Thomas J.
PATENT ASSIGNEE(S): Health Research, Inc., USA
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1238666	A2	20020911	EP 2002-4592	20020228 <--
EP 1238666	A3	20040107		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002128303	A1	20020912	US 2001-801163	20010307 <--
US 6495585	B2	20021217		
JP 2002325853	A2	20021112	JP 2002-61784	20020307 <--
PRIORITY APPLN. INFO.:			US 2001-801163 A	20010307 <--

AB A novel method for treating undesired hyperproliferative tissue in a mammal. The method includes the steps of: injecting the mammal with a photodynamic compound having a selective uptake in the hyperproliferative tissue and which is activated at a particular light frequency; injecting the mammal with a xanthenone-4-acetic acid or a Group I metal, Group II metal or quaternary salt thereof near the time of maximum uptake of the photodynamic compound in the hyperproliferative tissue; and exposing the hyperproliferative tissue to light at the particular frequency that activates the photodynamic compound The method of the invention causes necrosis of the hyperproliferative tissue to an extent greater than can be obtained by either the photodynamic compound or xanthenone-4-acetic acid alone. Further and surprisingly the method enhances immune response of the mammal to the hyperproliferative tissue even after the photodynamic compound and xanthenone-4-acetic acid are no longer present in the mammal. Efficacy of a **combination** of 20 mg 5,6-dimethylxanthenone-4-acetic acid and 135 J/cm2 630 nm laser light against RIF-1 tumors in mice is shown.

IC ICM A61K031-352
ICS A61K049-00; A61P035-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
IT **Antitumor agents**
Neoplasm
Photodynamic therapy
(use of xanthenone acetic acid in treatment of hyperproliferative disorders)
IT 35614-21-2D, Xanthenone-4-acetic acid, derivs. **117570-53-3**, 5,6-Dimethylxanthenone-4-acetic acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of xanthenone acetic acid in treatment of hyperproliferative disorders)

L35 ANSWER 7 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2002698170 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12459380
TITLE: **Combination** of vascular targeting agents with thermal or radiation therapy.
AUTHOR: Horsman Michael R; Murata Rumi
CORPORATE SOURCE: Department of Experimental Clinical Oncology, Aarhus

University Hospital, Aarhus, Denmark.. mike@onclology.dk
SOURCE: International journal of radiation oncology, biology, physics, (2002 Dec 1) 54 (5) 1518-23.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030103
Entered Medline: 20030102

AB PURPOSE: The most likely clinical application of vascular targeting agents (VTAs) is in **combination** with more conventional therapies. In this study, we report on preclinical studies in which VTAs were **combined** with hyperthermia and/or radiation. METHODS AND MATERIALS: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was treated when at 200 mm3 in size. The VTAs were combretastatin A-4 disodium phosphate (CA4DP, 25 mg/kg), flavone acetic acid (FAA, 150 mg/kg), and 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**, 20 mg/kg), and were all injected i.p. Hyperthermia and radiation were locally administered to tumors of restrained, nonanesthetized mice, and response was assessed using either a tumor growth or tumor control assay. RESULTS: Heating tumors at 41.5 degrees C gave rise to a linear relationship between the heating time and tumor growth with a slope of 0.02. This slope was increased to 0.06, 0.09, and 0.08, respectively, by injecting the VTAs either 30 min (CA4DP), 3 h (FAA), or 6 h (**DMXAA**) before heating. The radiation dose (+/-95% confidence interval) that controls 50% of treated tumors (the TCD(50) value) was estimated to be 53 Gy (51-55 Gy) for radiation alone. This was decreased to 48 Gy (46-51 Gy), 45 Gy (41-49 Gy), and 42 Gy (39-45 Gy), respectively, by injecting CA4DP, **DMXAA**, or FAA 30-60 min after irradiating. These values were further decreased to around 28-33 Gy if the tumors of VTA-treated mice were also heated to 41.5 degrees C for 1 h, starting 4 h after irradiation, and this effect was much larger than the enhancement seen with either 41.5 degrees C or even 43 degrees C alone. CONCLUSIONS: Our preclinical studies and those of others clearly demonstrate that VTAs can enhance tumor response to hyperthermia and/or radiation and support the concept that such **combination** studies should be undertaken clinically for the full potential of VTAs to be realized.

CT Check Tags: Support, Non-U.S. Gov't
Adjuvants, Immunologic: TU, therapeutic use
Animals
Antineoplastic Agents: TU, therapeutic use
Antineoplastic Agents, Phytogenic: TU, therapeutic use
Dose-Response Relationship, Radiation
Flavonoids: TU, therapeutic use
*Hyperthermia, Induced: MT, methods
Mice
Mice, Inbred C3H
Neoplasm Transplantation
*Neoplasms: RT, radiotherapy
*Neoplasms: TH, therapy
*Neovascularization, Pathologic
Stilbenes: TU, therapeutic use
Temperature
Time Factors
Tumor Cells, Cultured
X-Rays

Xanthenes: TU, therapeutic use
***Xanthones**
RN 117048-59-6 (combretastatin A-4); **117570-53-3 (5,6-dimethylxanthenoneacetic acid)**; 87626-55-9 (flavone acetic acid)
CN 0 (Adjuvants, Immunologic); 0 (Antineoplastic Agents); 0 (Antineoplastic Agents, Phytogenic); 0 (Flavonoids); 0 (Stilbenes); 0 (Xanthenes); 0 (Xanthones)

L35 ANSWER 8 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2002446445 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12201491
TITLE: 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**): a new biological response modifier for cancer therapy.
AUTHOR: Zhou Shufeng; Kestell Philip; Baguley Bruce C; Paxton James W
CORPORATE SOURCE: Division of Pharmacology and Clinical Pharmacology, Faculty of Medical and Health Sciences, University ofAuckland, New Zealand.. shufeng.zhou@auckland.ac.nz
SOURCE: Investigational new drugs, (2002 Aug) 20 (3) 281-95. Ref: 75
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020904
Last Updated on STN: 20030406
Entered Medline: 20030404

AB The investigational anti-cancer drug 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) was developed by the Auckland Cancer Society Research Centre (ACSRC). It has recently completed Phase I trials in New Zealand and UK under the direction of the Cancer Research Campaign's Phase I/II Clinical Trials Committee. As a biological response modifier, pharmacological and toxicological properties of **DMXAA** are remarkably different from most conventional chemotherapeutic agents. Induction of cytokines (particularly tumour necrosis factor (TNF-alpha), serotonin and nitric oxide (NO)), anti-vascular and anti-angiogenic effects are considered to be major mechanisms of action based on in vitro and animal studies. In cancer patients of Phase I study, **DMXAA** also exhibited various biological effects, including induction of TNF-alpha, serotonin and NO, which are consistent with those effects observed in in vitro and animal studies. Preclinical studies indicated that **DMXAA** had more potent anti-tumour activity compared to flavone-8-acetic acid (FAA). In contrast to FAA that did not show anti-tumour activity in cancer patients, **DMXAA** (22 mg/kg by intravenous infusion over 20 min) resulted in partial response in one patient with metastatic cervical squamous carcinoma in a Phase I study where 65 cancer patients were enrolled in New Zealand. The maximum tolerated dose (MTD) in mouse, rabbit, rat and human was 30, 99, 330, and 99 mg/kg respectively. The dose-limiting toxicity of **DMXAA** in cancer patients included acute reversible tremor, cognitive impairment, visual disturbance, dyspnoea and anxiety. The plasma protein binding and distribution into blood cells of **DMXAA** are dependent on species and drug concentration. **DMXAA** is extensively metabolised, mainly by glucuronidation of its acetic acid side chain and 6-methylhydroxylation, giving rise to **DMXAA** acyl glucuronide (

DMXAA-G), and 6-hydroxymethyl-5-methylxanthenone-4-acetic acid (6-OH-MXAA), which are excreted into bile and urine. **DMXAA**-G has been shown to be chemically reactive, undergoing hydrolysis, intramolecular migration and covalent binding. Studies have indicated that **DMXAA** glucuronidation is catalysed by uridine diphosphate glucuronosyltransferases (UGT1A9 and UGT2B7), and 6-methylhydroxylation by cytochrome P450 (CYP1A2). Non-linear plasma pharmacokinetics of **DMXAA** has been observed in animals and patients, presumably due to saturation of the elimination process and plasma protein binding. Species differences in **DMXAA** plasma pharmacokinetics have been observed, with the rabbit having the greatest plasma clearance, followed by the human, rat and mouse. In vivo disposition studies in these species did not provide an explanation for the differences in MTD. Co-administration of **DMXAA** with other drugs has been shown to result in enhanced anti-tumour activity and alterations in pharmacokinetics, as reported for the **combination** of **DMXAA** with melphalan, thalidomide, cyproheptadine, and the bioreductive agent tirapazamine, in mouse models. Species-dependent **DMXAA**-thalidomide pharmacokinetic interactions have been observed. Co-administration of thalidomide significantly increased the plasma area of the plasma concentration-time curve (AUC) of **DMXAA** in mice, but had no effect on **DMXAA**'s pharmacokinetics in the rat. It appears that the pharmacological and toxicological properties of **DMXAA** as a new biological response modifier are unlikely to be predicted based on preclinical studies. Similar to many biological response modifiers, **DMXAA** alone did not show striking anti-tumour activity in patients. However, preclinical studies of **DMXAA**-drug **combinations** indicate that **DMXAA** may have a potential role in cancer treatment when co-administered with other drugs. Further studies are required to explore the molecular targets of **DMXAA** and mechanisms for the interactions with other drugs co-administered during **combination** treatment, which may allow for the optimisation of **DMXAA**-based chemotherapy.

CT Check Tags: Human
Animals
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
*Biological Response Modifiers: PD, pharmacology
Biological Response Modifiers: TU, therapeutic use
Drug Interactions
*Neoplasms: DT, drug therapy
Neoplasms: PA, pathology
Xanthenes: AE, adverse effects
Xanthenes: PK, pharmacokinetics
*Xanthenes: PD, pharmacology
Xanthenes: TU, therapeutic use
***Xanthones**

RN **117570-53-3 (5,6-dimethylxanthenoneacetic acid)**

CN 0 (Antineoplastic Agents); 0 (Biological Response Modifiers); 0 (Xanthenes); 0 (Xanthones)

L35 ANSWER 9 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2002135262 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11870905
TITLE: Differential sensitivity of two adenocarcinoma xenografts to the anti-vascular drugs combretastatin A4 phosphate and 5,6-**dimethylxanthenone**-4-acetic acid, assessed using MRI and MRS.
AUTHOR: Beauregard Daniel A; Pedley R Barbara; Hill Sally A; Brindle Kevin M

CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge CB2 1GA, UK.
SOURCE: NMR in biomedicine, (2002 Apr) 15 (2) 99-105.
Journal code: 8915233. ISSN: 0952-3480.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020301
Last Updated on STN: 20020621
Entered Medline: 20020620

AB The effects of two anti-vascular agents, combretastatin A4 phosphate (CA4P), and 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**), on the perfusion of two human colon adenocarcinomas implanted in SCID mice, were assessed for up to 3 h using non-invasive magnetic resonance imaging (MRI) and spectroscopy techniques (MRS). MRI measurements of GdDTPA inflow showed that treatment with CA4P had little effect on the perfusion of HT29 tumours. Localized (31)P MRS measurements also showed that the drug had no significant effect on tumour cell energy status, as assessed from the ratio of the integrals of the signals from inorganic phosphate (P(i)) and nucleoside triphosphates. However, after treatment with **DMXAA**, perfusion was reduced and the P(i)/NTP ratio increased, indicating that the HT29 tumour is susceptible to the action of this drug. The LS174T tumour model was susceptible to both CA4P and **DMXAA**, using the criteria of changes in GdDTPA inflow and P(i)/NTP ratio.

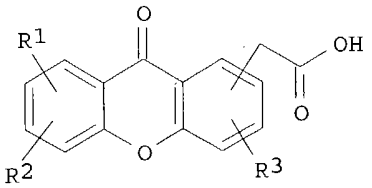
CT Check Tags: Human; Support, Non-U.S. Gov't
Adenocarcinoma: BS, blood supply
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PA, pathology
*Angiogenesis Inhibitors: TU, therapeutic use
Animals
Antineoplastic Agents: TU, therapeutic use
*Antineoplastic Agents, Phytogenic: TU, therapeutic use
***Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use**
Colonic Neoplasms: BS, blood supply
*Colonic Neoplasms: DT, drug therapy
Colonic Neoplasms: PA, pathology
Contrast Media
Gadolinium DTPA
Magnetic Resonance Imaging
Magnetic Resonance Spectroscopy
Mice
Mice, SCID
*Stilbenes: TU, therapeutic use
Transplantation, Heterologous
*Xanthenes: TU, therapeutic use
***Xanthones**
RN 117048-59-6 (combretastatin A-4); **117570-53-3 (5,6-dimethylxanthenoneacetic acid)**; 80529-93-7 (Gadolinium DTPA)
CN 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents); 0 (Antineoplastic Agents, Phytogenic); 0 (Antineoplastic **Combined** Chemotherapy Protocols); 0 (Contrast Media); 0 (Stilbenes); 0 (Xanthenes); 0 (Xanthones)

L35 ANSWER 10 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:664509 HCAPLUS

DOCUMENT NUMBER: 135:221279
TITLE: **Combination** of xanthenone derivatives and paclitaxel or docetaxel for treatment of cancer
INVENTOR(S): Wilson, William Robert
PATENT ASSIGNEE(S): Auckland UniServices Limited, N. Z.
SOURCE: Jpn. Kokai Tokkyo Koho, 22 pp.
CODEN: JKXXAF
DOCUMENT TYPE: **Patent**
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001247459	A2	20010911	JP 2000-232871	20000801 <--
US 2001027210	A1	20011004	US 2001-774002	20010131 <--
US 6667337	B2	20031223		
PRIORITY APPLN. INFO.:			NZ 2000-503199 A	20000303 <--

GI



I

AB Xanthenone derivs. (I; R1, R2, R3 = H, C1-5 alkyl, halogen, CF3, CN, NO2, NH2, OH, OR, NHCOR, NHSO2R, SR, SO2R, NHR, with R = (substituted)alkyl) and their pharmaceutically acceptable salts in **combination** with paclitaxel or docetaxel are claimed for treatment of cancer. The synergistic antitumor effects of the **combinations** were tested in mice.

IC ICM A61K031-352
ICS A61P035-00; C07D311-86; A61K031-352; A61K031-337

CC 1-6 (Pharmacology)

ST xanthenone deriv paclitaxel docetaxel **combination** antitumor

IT **Antitumor agents**
(**combination** of xanthenone derivs. and paclitaxel or docetaxel for treatment of cancer)

IT Drug interactions
(synergistic; **combination** of xanthenone derivs. and paclitaxel or docetaxel for treatment of cancer)

IT 90-47-1D, Xanthenone, derivs. 33069-62-4, Paclitaxel 114977-28-5, Docetaxel **117570-53-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**combination** of xanthenone derivs. and paclitaxel or docetaxel for treatment of cancer)

L35 ANSWER 11 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:184772 BIOSIS

DOCUMENT NUMBER: PREV200100184772
TITLE: Vascular attack by 5,6-**dimethylxanthenone** -4-acetic acid **combined** with B7.1 (CD80)-mediated immunotherapy overcomes immune resistance and leads to the eradication of large **tumors** and multiple **tumor** foci.
AUTHOR(S): Kanwar, Jagat R.; Kanwar, Rupinder K.; Pandey, Sushil; Ching, Lai-Ming; Krissansen, Geoffrey W. [Reprint author]
CORPORATE SOURCE: Department of Molecular Medicine, School of Medicine and Health Science, University of Auckland, 85 Park Road, Grafton, Auckland, New Zealand
gw.krissansen@auckland.ac.nz
SOURCE: Cancer Research, (March 1, 2001) Vol. 61, No. 5, pp. 1948-1956. print.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Apr 2001
Last Updated on STN: 18 Feb 2002

AB The promise of **cancer** immunotherapy is that it will not only eradicate primary **tumors** but will generate systemic **antitumor** immunity capable of destroying distant metastases. A major problem that must first be surmounted relates to the immune resistance of large **tumors.** Here we reveal that immune resistance can be overcome by **combining** immunotherapy with a concerted attack on the **tumor** vasculature. The functionally related **antitumor** drugs 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**) and flavone acetic acid (FAA), which cause **tumor** vasculature collapse and **tumor** necrosis, were used to attack the **tumor** vasculature, whereas the T-cell costimulator B7.1 (CD80), which costimulates T-cell proliferation via the CD28 pathway, was used to stimulate **antitumor** immunity. The injection of cDNA (60-180 mug) encoding B7.1 into large EL-4 **tumors** (0.8 cm in diameter) established in C57BL/6 mice, followed 24 h later by i.p. administration of either **DMXAA** (25 mg/kg) or FAA (300 mg/kg), resulted in complete **tumor** eradication within 2-6 weeks. In contrast, monotherapies were ineffective. Both vascular attack and B7.1 immunotherapy led to up-regulation of heat shock protein 70 on stressed and dying **tumor** cells, potentially augmenting immunotherapy. Remarkably, large **tumors** took on the appearance of a wound that rapidly ameliorated, leaving perfectly healed skin. **Combined** therapy was mediated by CD8+ T cells and natural killer cells, accompanied by heightened and prolonged **antitumor** cytolytic activity ($P < 0.001$), and by a marked increase in **tumor** cell apoptosis. Cured animals completely rejected a challenge of 1 X 107 parental EL-4 **tumor** cells but not a challenge of 1 X 104 Lewis lung carcinoma cells, demonstrating that **antitumor** immunity was **tumor** specific. Adoptive transfer of 2 X 108 splenocytes from treated mice into recipients bearing established (0.8 cm in diameter) **tumors** resulted in rapid and complete **tumor** rejection within 3 weeks. Although **DMXAA** and B7.1 monotherapies are complicated by a narrow range of effective doses, **combined** therapy was less dosage dependent. Thus, a broad range of amounts of B7.1 cDNA were effective in **combination** with 25 mg/kg **DMXAA** . In contrast, **DMXAA**, which has a very narrow range of high active doses, was effective at a low dose (18 mg/kg) when administered with a large amount (180 mug) of B7.1 cDNA. Importantly, **combinational** therapy generated heightened **antitumor** immunity, such that gene transfer of B7.1 into one **tumor**, followed by systemic **DMXAA** treatment, led to the complete

rejection of multiple untreated **tumor** nodules established in the opposing flank. These findings have important implications for the future direction and utility of **cancer** immunotherapies aimed at harnessing patients' immune responses to their own **tumors.**

CC Neoplasms - Therapeutic agents and therapy 24008
Cytology - Animal 02506
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - Immunological processes and allergy 22018
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; **Tumor** Biology

IT Parts, Structures, & Systems of Organisms
T-cell: blood and lymphatics, immune system, proliferation

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug; B7.1 [CD80]: immunostimulant; flavone acetic acid: **antineoplastic**-drug

IT Methods & Equipment
cancer immunotherapy: therapeutic method; gene transfer: therapeutic method

IT Miscellaneous Descriptors
apoptosis; immune resistance; immunity; **tumor** vasculature

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
EL-4 cell line: thymic lymphoma
mouse: C57BL/6
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
87626-55-9 (flavone acetic acid)

L35 ANSWER 12 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2001:392335 BIOSIS
DOCUMENT NUMBER: PREV200100392335
TITLE: A difference between the rat and mouse in the pharmacokinetic interaction of 5,6-**dimethylxanthenone**-4-acetic acid with thalidomide.
AUTHOR(S): Zhou, Shufeng; Kestell, Philip; Tingle, Malcolm D.; Ching, Lai-Ming; Paxton, James W. [Reprint author]
CORPORATE SOURCE: Department of Pharmacology and Clinical Pharmacology, The University of Auckland School of Medicine, Auckland, New Zealand
j.paxton@auckland.ac.nz
SOURCE: Cancer Chemotherapy and Pharmacology, (June, 2001) Vol. 47, No. 6, pp. 541-544. print.
CODEN: CCPHDZ. ISSN: 0344-5704.
DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 15 Aug 2001
Last Updated on STN: 22 Feb 2002

AB Purpose: Coadministration of thalidomide, cyproheptadine or diclofenac has been shown to increase the area under the plasma concentration-time curve (AUC) of the novel **antitumour** agent 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) in mice. The aim of this study was to further investigate these pharmacokinetic **DMXAA**-drug interactions in the rat model. Methods: The effects of coadministration of L-thalidomide, cyproheptadine or diclofenac on the pharmacokinetics of **DMXAA** were investigated in male Wistar Kyoto rats. The effects of L-thalidomide, cyproheptadine and diclofenac on microsomal metabolism and plasma protein binding of **DMXAA** were also investigated. Results: No significant alteration in the plasma concentration profile for **DMXAA** was observed following L-thalidomide pretreatment in rats. In contrast, when **combined** with diclofenac or cyproheptadine, the plasma AUC of **DMXAA** was significantly ($P < 0.05$) increased by 48% and 88% and the T1/2 by 36% and 107%, respectively, compared to controls. Both diclofenac and cyproheptadine at 500 muM caused a significant inhibition of **DMXAA** metabolism in rat liver microsomes. In contrast, L-thalidomide had no or little inhibitory effect on **DMXAA** metabolism in rat liver microsomes except for causing a 32% decrease in 6-methylhydroxylation at 500 muM. None of the drugs had a significant effect on the plasma protein binding of **DMXAA** in the rat. Conclusion: These studies showed that coadministration of L-thalidomide did not alter the plasma **DMXAA** AUC in rats, in contrast to previous studies in mice, whereas diclofenac and cyproheptadine significantly reduced the plasma clearance of **DMXAA** in rats in a similar manner to their effect in mice. The cause of the species difference in the pharmacokinetic response to thalidomide by **DMXAA** is unknown, and indicates difficulties in predicting the outcome of such a **combination** in patients.

CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Pharmacology

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, pharmacokinetics; L-thalidomide; cyproheptadine; diclofenac

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Wistar rat: male
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
129-03-3 (cyproheptadine)
15307-86-5 (diclofenac)

L35 ANSWER 13 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 1
ACCESSION NUMBER: 2001:578258 BIOSIS

DOCUMENT NUMBER: PREV200100578258
TITLE: Potentiation of the anti-**tumour** effect of hyperthermia by **combining** with the vascular targeting agent 5,6-**dimethylxanthenone**-4-acetic acid.
AUTHOR(S): Murata, R. [Reprint author]; Overgaard, J.; Horsman, M. R.
CORPORATE SOURCE: Department of Experimental Clinical Oncology, Danish Cancer Society, Aarhus University Hospital, Norrebrogade 44, Building 5, DK-8000, Aarhus, Denmark
rumi@oncology.dk
SOURCE: International Journal of Hyperthermia, (November-December, 2001) Vol. 17, No. 6, pp. 508-519. print.
CODEN: IJHYEQ. ISSN: 0265-6736.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 2001
Last Updated on STN: 25 Feb 2002

AB The potential of the vascular targeting agent 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) to enhance the effect of hyperthermia was investigated in a C3H mouse mammary carcinoma grown in the feet of female CDF1 mice and in normal foot skin. **DMXAA**, when injected intraperitoneally in restrained non-anaesthetized animals, reduced **tumour** perfusion, as measured using the RbCl extraction procedure, and increased necrosis in histological section, but these effects were dependent on the drug dose and time interval. At a dose of 20 mg/kg, it significantly enhanced the thermal damage of this **tumour**, when given 1 h or more before the start of heating, as assessed by a **tumour** growth assay. This enhancement became larger with increasing interval between the two treatments. No thermo-potentiation was seen at doses of 10 mg/kg or lower. These **combined** effects seem to be associated with the **tumour** vascular shut-down by **DMXAA.** Thermal potentiation by **DMXAA** was also dependent on the heating temperature, with a greater enhancement relative to hyperthermia alone obtained at the lower temperatures at 40.5 and 41.5degreeC than at the higher temperature of 42.5degreeC. **DMXAA** (20 mg/kg) also enhanced the heat damage of normal skin, and this could not be explained by any **DMXAA**-induced TNF-alpha production. The heat enhancement-ratio by **DMXAA** was larger in **tumours** (1.9) than in normal skin (1.3-1.5), thus giving rise to a therapeutic gain.

CC Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Endocrine - General 17002
Integumentary system - Physiology and biochemistry 18504
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Methods and Techniques; Pharmacology; **Tumor** Biology

IT Parts, Structures, & Systems of Organisms
foot skin: integumentary system; mammary carcinoma **tumor**, necrosis, perfusion

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid [**DMXAA**]: **antineoplastic**-drug, dose, intraperitoneal injection, vascular targeting agent; **tumor** necrosis factor-alpha [TNF-alpha]

IT Methods & Equipment
hyperthermia: anti-**tumor** effect, heating temperature, therapeutic method; rubidium chloride extraction procedure: measurement

method; **tumor** growth assay: assessment method
IT Miscellaneous Descriptors
thermal potentiation; time interval
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C3H cell line: mouse mammary carcinoma cells
mouse: animal model, female, strain-CDF1
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
117570-53-3 (**DMXAA**)

L35 ANSWER 14 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 2
ACCESSION NUMBER: 2001:577131 BIOSIS
DOCUMENT NUMBER: PREV200100577131
TITLE: Improved **tumor** response by **combining** radiation and the vascular-damaging drug 5,6-**dimethylxanthenone**-4-acetic acid.
AUTHOR(S): Murata, Rumi [Reprint author]; Siemann, Dietmar W.; Overgaard, Jens; Horsman, Michael R.
CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Norrebrogade 44, Building 5, DK-8000, Aarhus C, Denmark rumi@oncology.dk
SOURCE: Radiation Research, (November, 2001) Vol. 156, No. 5 Part 1, pp. 503-509. print.
CODEN: RAREAE. ISSN: 0033-7587.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 2001
Last Updated on STN: 25 Feb 2002

AB The interaction between 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) and radiation was investigated in two different mouse **tumor** models and a normal mouse tissue. C3H mouse mammary carcinomas transplanted in the feet of CDF1 mice and KHT mouse sarcomas growing in the leg muscles of C3H/HeJ mice were used. **DMXAA** was dissolved in saline and injected intraperitoneally. **Tumors** were irradiated locally in nonanesthetized mice, and response was assessed using **tumor** growth for the C3H mammary carcinoma and in vivo/in vitro clonogenic cell survival for the KHT sarcoma. **DMXAA** alone had an **antitumor** effect in both **tumor** types, but only at doses above 15 mg/kg. **DMXAA** also enhanced radiation damage, and again there was a threshold dose. No enhancement was seen in the C3H mammary carcinoma at 10 mg/kg and below, while in the KHT sarcoma, doses above 15 mg/kg were necessary. This enhancement of radiation damage was also dependent on the sequence of and interval between the treatments with **DMXAA** and radiation. **Combining** radiation with **DMXAA** at the maximum tolerated dose (i.e., the highest dose that could be injected without causing any lethality) of either 20 mg/kg (CDF1 mice) or 17.5 mg/kg (C3H/HeJ mice) gave an additive response when the two agents were administered simultaneously. Even greater **antitumor** effects were achieved when **DMXAA** was administered 1-3 h after irradiation. However, when administration of **DMXAA** preceded irradiation, the effect was similar to that seen for radiation alone, suggesting that appropriate timing is essential to maximize the utility of

this agent. When such conditions were met, **DMXAA** was found to increase the **tumor** response significantly in the absence of an enhancement of radiation damage in normal skin, thus giving rise to therapeutic gain.

CC Cytology - Animal 02506
Radiation biology - General 06502
Pathology - Therapy 12512
Integumentary system - Physiology and biochemistry 18504
Pharmacology - General 22002
Pharmacology - Cardiovascular system 22010
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Pharmacology; Radiation Biology; **Tumor** Biology

IT Parts, Structures, & Systems of Organisms
skin: integumentary system, damage

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid [**DMXAA**]: cardiovascular-drug

IT Methods & Equipment
mouse **tumor** model: analytical method, evaluation method; radiotherapy: therapeutic method

IT Miscellaneous Descriptors
clonogenic cell survival; radiation damage; therapeutic gain; timing; **tumor** response

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C3H cell line: mouse mammary carcinoma cells
KHT cell line: mouse sarcoma cells
mouse: strain-C3H/HeJ, strain-CDF1
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
117570-53-3 (**DMXAA**)

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ACCESSION NUMBER: 2001:172716 BIOSIS
DOCUMENT NUMBER: PREV200100172716
TITLE: Comparative effects of combretastatin A-4 disodium phosphate and 5,6-**dimethylxanthenone**-4-acetic acid on blood perfusion in a murine **tumour** and normal tissues.
AUTHOR(S): Murata, R. [Reprint author]; Overgaard, J.; Horsman, M. R.
CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Norrebrogade 44, Building 5, DK-8000, Aarhus C, Denmark rumi@oncology.dk
SOURCE: International Journal of Radiation Biology, (February, 2001) Vol. 77, No. 2, pp. 195-204. print.
CODEN: IJRBE7. ISSN: 0955-3002.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Apr 2001
Last Updated on STN: 18 Feb 2002

AB Purpose: To compare the ability of combretastatin A-4 disodium phosphate (CA4DP) and 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**

) to change tissue blood perfusion. Materials and methods: The tissues were a C3H mouse mammary carcinoma and various murine normal tissues, with perfusion measured using the 86RbCl extraction technique. Results: CA4DP (250 mg/kg; i.p.) reduced **tumour** perfusion to 34% of that seen in controls within 1 h of injection. It was maintained at this for at least 6 h, returning to control levels by 24 h. This decrease was dose-dependent. **DMXAA** (25 mg/kg; i.p.) caused a 79% reduction in **tumour** perfusion 6 h after injection; no recovery was observed even after 24 h. **DMXAA** showed no changes at doses below 10 mg/kg. Both CA4DP and **DMXAA** increased perfusion in the gut, kidney, bladder and lung, while decreasing splenic perfusion. CA4DP tended to decrease perfusion in muscle, while **DMXAA** increased liver perfusion. These changes in normal tissue perfusion were generally less than those changes seen in **tumours.** No significant changes were seen in skin. Conclusions: CA4DP and **DMXAA** produced a selective and significant reduction in **tumour** perfusion, but the pattern of change was different. These results suggest how these vascular targeting drugs should be **combined** with more conventional therapies.

CC Cytology - Animal 02506
Radiation biology - General 06502
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Pharmacology; Radiation Biology; **Tumor** Biology

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **tumor** blood perfusion disrupting agent, **tumor**-specific anti-vascular effects; combretastatin A-4 disodium phosphate: **tumor** blood perfusion disrupting agent, **tumor**-specific anti-vascular effects; ruthenium-86 chloride

IT Miscellaneous Descriptors
radiotherapeutic-hypothermia clinical applications; **tumor** blood perfusion

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C3H cell line: mouse mammary carcinoma cells
murine: normal tissues
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
168555-66-6 (combretastatin A-4 disodium phosphate)

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ACCESSION NUMBER: 2002:97928 BIOSIS
DOCUMENT NUMBER: PREV200200097928
TITLE: Measurement of plasma 5-hydroxyindoleacetic acid as a possible clinical surrogate marker for the action of antivascular agents.
AUTHOR(S): Kestell, Philip [Reprint author]; Zhao, Liangli; Jameson, Michael B.; Stratford, Michael R. L.; Folkes, Lisa K.; Baguley, Bruce C.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland Medical School, Auckland Hospital, Auckland, New

Zealand
p.kestell@auckland.ac.nz
SOURCE: Clinica Chimica Acta, (December, 2001) Vol. 314, No. 1-2, pp. 159-166. print.
CODEN: CCATAR. ISSN: 0009-8981.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 2002
Last Updated on STN: 25 Feb 2002

AB Background: Serotonin (5HT), a naturally occurring vasoactive substance, is released from platelets into plasma under various pathological conditions. Recently, **anticancer** drugs that act by selectively disrupting **tumour** blood flow have been found to increase plasma 5HT concentrations in mice. Two such antivascular agents, flavone acetic acid (FAA) and 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**), have completed Phase I clinical trial and raise the important question of whether suitable surrogate markers for antivascular effects can be identified. Methods: 5HT is unstable to storage, precluding routine clinical assay, but the 5HT metabolite, 5-hydroxyindoleacetic acid (5HIAA) accumulates in plasma following 5HT release and is a more suitable marker because of its greater stability. We have developed an automated procedure for the assay of the low concentrations of 5HIAA found in humans by **combining** solid-phase extraction with high-performance liquid chromatography (HPLC). Results: Efficient separation of 5HIAA from possible interfering substances in human plasma, including a variety of pharmaceutical agents, was achieved on C18 columns using cetyltrimethylammonium bromide (CETAB) as an organic modifier. Adequate precision, accuracy and sensitivity were achieved by electrochemical detection (ECD) at +400 mV. Analysis of plasma from two patients treated with **DMXAA** in a Phase I trial demonstrated **DMXAA**-induced elevation of plasma 5HIAA with a time course similar to that previously described in mice. Conclusions: Measurement of changes in plasma 5HIAA provides a new approach to the monitoring of therapies with an antivascular effect. The assay is sensitive to dietary sources of 5HT, which should be minimised.

CC Clinical biochemistry - General methods and applications 10006
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Endocrine - Neuroendocrinology 17020
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Clinical Chemistry (Allied Medical Sciences); Methods and Techniques; Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Parts, Structures, & Systems of Organisms
plasma: blood and lymphatics

IT Diseases
cancer: **neoplastic** disease
Neoplasms (MeSH)

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, Phase I clinical trial, antivascular agent; 5-hydroxyindoleacetic acid

IT Methods & Equipment
electrochemical detection: analytical method; high-performance liquid chromatography: analytical method; solid-phase extraction: separation

method
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
54-16-0 (5-hydroxyindoleacetic acid)

L35 ANSWER 17 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:414961 BIOSIS
DOCUMENT NUMBER: PREV200100414961
TITLE: Effects of **anticancer** drugs on the metabolism of the **anticancer** drug 5,6-**dimethylxanthenone**-4-acetic (**DMXAA**) by human liver microsomes.
AUTHOR(S): Zhou, Shufeng; Chin, Rebecca; Kestell, Philip; Tingle, Malcolm D.; Paxton, James W. [Reprint author]
CORPORATE SOURCE: Department of Pharmacology and Clinical Pharmacology, University of Auckland School of Medicine, Auckland, New Zealand
j.paxton@auckland.ac.nz
SOURCE: British Journal of Clinical Pharmacology, (August, 2001) Vol. 52, No. 2, pp. 129-136. print.
CODEN: BCPHBM. ISSN: 0306-5251.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Aug 2001
Last Updated on STN: 22 Feb 2002

AB Aims: To investigate the effects of various **anticancer** drugs on the major metabolic pathways (glucuronidation and 6-methylhydroxylation) of **DMXAA** in human liver microsomes. Methods: The effects of various **anticancer** drugs at 100 and 500 muM on the formation of **DMXAA** acyl glucuronide (**DMXAA**-G) and 6-hydroxymethyl-5-**methylxanthenone**-4-acetic acid (6-OH-MXAA) in human liver microsomes were determined by high performance liquid chromatography (h.p.l.c.). For those **anticancer** drugs showing significant inhibition of **DMXAA** metabolism, the inhibition constants (Ki) were determined. The resulting in vitro data were extrapolated to predict in vivo changes in **DMXAA** pharmacokinetics. Results: Vinblastine, vincristine and amsacrine at 500 muM significantly ($P<0.05$) inhibited **DMXAA** glucuronidation (Ki=319, 350 and 230 muM, respectively), but not 6-methylhydroxylation in human liver microsomes. Daunorubicin and N-(2-(dimethylamino)-ethyl)acridine-4-carboxamide (DACA) at 100 and 500 muM showed significant ($P<0.05$) inhibition of **DMXAA** 6-methylhydroxylation (Ki=131 and 0.59 muM, respectively), but not glucuronidation. Other drugs such as 5-fluoroucacil, paclitaxel, tirapazamine and methotrexate exhibited little or negligible inhibition of the metabolism of **DMXAA.** Pre-incubation of microsomes with the **anticancer** drugs (100 and 500 muM) did not enhance their inhibitory effects on **DMXAA** metabolism. Prediction of **DMXAA**-drug interactions in vivo based on these in vitro data indicated that all the **anticancer** drugs investigated except DACA appear unlikely to alter the pharmacokinetics of **DMXAA**, whereas DACA may increase the plasma AUC of **DMXAA** by 6%. Conclusions: These results indicate that alteration of the pharmacokinetics of

DMXAA appears unlikely when used in **combination** with other common **anticancer** drugs. However, this does not rule out the possibility of pharmacokinetic interactions with other drugs used concurrently with this **combination** of **anticancer** drugs.

CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Metabolism; Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic**-drug; 5,6-**dimethylxanthenone**-4-acetic acyl glucuronide: **antineoplastic**-drug; 6-hydroxymethyl-5-**methylxanthenone**-4-acetic acid; amsacrine: **antineoplastic**-drug; **anticancer** drugs; liver microsomes; vinblastine: **antineoplastic**-drug; vincristine: **antineoplastic**-drug

IT Miscellaneous Descriptors
6-methylhydroxylation; drug interaction; glucuronidation; inhibition constants

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
223261-32-3 (6-hydroxymethyl-5-**methylxanthenone**-4-acetic acid)
51264-14-3 (amsacrine)
865-21-4 (vinblastine)
57-22-7 (vincristine)

L35 ANSWER 18 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2000:235866 BIOSIS
DOCUMENT NUMBER: PREV200000235866
TITLE: Enhanced **antitumor** efficacy through the **combination** of vascular targeting agents and conventional **anticancer** drugs.
AUTHOR(S): Siemann, Dietmar W. [Reprint author]; Taylor, Destry; Lepler, Sharon; Rojiani, Amyn
CORPORATE SOURCE: H Lee Moffitt Cancer Ctr, Tampa, FL, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 525. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002
CC Pharmacology - General 22002

Cardiovascular system - General and methods 14501
Reproductive system - General and methods 16501
Neoplasms - General 24002
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Pharmacology; **Tumor** Biology
IT Parts, Structures, & Systems of Organisms
neovasculature: circulatory system
IT Chemicals & Biochemicals
cisplatin: **antineoplastic**-drug, **combination** therapy; combrestatin A-4 disodium phosphate: **antineoplastic**-drug, **combination** therapy, dosage, vascular targeting agent; cyclophosphamide: **antineoplastic**-drug, **combination** therapy; **dimethylxanthenone** acetic acid: **antineoplastic**-drug, **combination** therapy, dosage, vascular targeting agent
IT Miscellaneous Descriptors
necrosis; Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
OW1 cell line: human ovarian **cancer** cells
SKBR3 cell line: human breast **cancer** cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Rodentia 86265
Super Taxa
Mammalia; Vertebrata; Chordata; Animalia
Organism Name
KHT cell line: rodent sarcoma cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 15663-27-1 (cisplatin)
50-18-0 (cyclophosphamide)

L35 ANSWER 19 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:414241 BIOSIS
DOCUMENT NUMBER: PREV200000414241
TITLE: Modulation of the pharmacokinetics of the **antitumour** agent 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) in mice by thalidomide.
AUTHOR(S): Kestell, Philip; Zhao, Liangli; Baguley, Bruce C.; Palmer, Brian D.; Muller, George; Paxton, James W.; Ching, Lai-Ming [Reprint author]
CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland Medical School, Auckland, New Zealand
SOURCE: Cancer Chemotherapy and Pharmacology, (August, 2000) Vol. 46, No. 2, pp. 135-141. print.
CODEN: CCPHDZ. ISSN: 0344-5704.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 2000
Last Updated on STN: 8 Jan 2002
AB Background: 5,6-**Dimethylxanthenone**-4-acetic acid (**DMXAA**), an investigative drug currently in clinical trial, acts on

tumour vasculature through the induction of cytokines. Coadministration of thalidomide, a modulator of cytokine production, potentiates the **antitumour** activity of **DMXAA** against the murine Colon 38 carcinoma in mice. We wished to determine whether alteration of the pharmacokinetics of **DMXAA** by thalidomide could provide an explanation for this potentiation. Results: Coadministration of thalidomide to Colon 38 **tumour**-bearing mice significantly ($P < 0.05$) increased the elimination half-life (t1/2) of **DMXAA** in plasma (413 mumol/l), liver (132 mumol/l), and spleen (77 mumol/l), and significantly ($P < 0.05$) increased **DMXAA** concentrations in Colon 38 **tumour** tissue (0.25-4.5 h). L-Thalidomide had a greater effect on **DMXAA** elimination ($P < 0.01$) than did D-thalidomide or the racemate. Coadministration of thalidomide increased the area under the concentration-time curve (AUC) of **DMXAA** by 1.8-fold in plasma, liver and spleen, and by 3.0-fold in **tumour.** Bile from mice given thalidomide and **DMXAA** contained substantially lower amounts of the glucuronide metabolite of **DMXAA** (**DMXAA** -G) than did bile from mice given **DMXAA** alone. Conclusion: Glucuronidation is a major excretory pathway for **DMXAA** in the mouse. Thalidomide, probably as the L-form, decreases the rate of elimination of **DMXAA** from plasma, spleen, liver and **tumour** by altering the rate of glucuronidation. The reduction in the elimination of **DMXAA** by thalidomide may lead to a selective increase in exposure of **tumour** tissue to drug, providing a basis for its potentiation of **antitumour** activity.

CC Digestive system - Physiology and biochemistry 14004
Cytology - Animal 02506
Biochemistry studies - General 10060
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Parts, Structures, & Systems of Organisms
liver: digestive system; spleen: blood and lymphatics, immune system

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, **combination** therapy, pharmacokinetics, plasma; 5,6-**dimethylxanthenone**-4-acetic acid glucuronide metabolite; thalidomide: **antineoplastic**-drug, **combination** therapy

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Colon 38 cell line: murine carcinoma cell
mouse: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
50-35-1 (thalidomide)

L35 ANSWER 20 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:212042 BIOSIS
DOCUMENT NUMBER: PREV200000212042
TITLE: **Tumor** ablation by **combined** antibody-directed and antivascular therapy.
AUTHOR(S): Pedley, R. Barbara [Reprint author]; Sharma, Surinder K.; Hill, Sally A.; Boden, Robert; Boxer, Geoffrey M.; Flynn, Aiden A.; Springer, Caroline J.; Begent, Richard H. J.
CORPORATE SOURCE: Gray Lab Cancer Res Trust, Northwood, UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 79. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 May 2000
Last Updated on STN: 5 Jan 2002
CC Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; **Tumor** Biology
IT Diseases
solid **tumors**: **neoplastic** disease
Neoplasms (MeSH)
IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, antivascular agent; combretastatin A4-P: **antineoplastic** -drug, antivascular agent
IT Methods & Equipment
antitumor antibodies localize therapy: therapeutic method; antivascular therapy: therapeutic method; phosphor image analysis: analytical method
IT Miscellaneous Descriptors
tumor ablation; Meeting Abstract
RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 21 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:368433 BIOSIS
DOCUMENT NUMBER: PREV200000368433
TITLE: **Tumour** eradication by **combined** antibody-directed and antivascular therapy.
AUTHOR(S): Pedley, R. B. [Reprint author]; Sharma, S. K. [Reprint author]; Boxer, G. [Reprint author]; Flynn, A. A. [Reprint author]; Boden, R. [Reprint author]; Watson, R. [Reprint author]; Dearling, J. [Reprint author]; Hill, S. A.; Springer, C. J.; Begent, R. H. J. [Reprint author]
CORPORATE SOURCE: Oncology Dept, RF and UCLMS, London, NW32PF, UK
SOURCE: British Journal of Cancer, (July, 2000) Vol. 83, No. Supplement 1, pp. 13. print.
Meeting Info.: Meeting of the British Cancer Research.

Brighton, UK. July 09-12, 2000.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 2000
Last Updated on STN: 8 Jan 2002
CC Digestive system - Pathology 14006
General biology - Symposia, transactions and proceedings 00520
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Cardiovascular system 22010
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Pharmacology; **Tumor** Biology
IT Diseases
colorectal **cancer**: digestive system disease, **neoplastic** disease, in-vivo xenograft study, treatment
Colorectal **Neoplasms** (MeSH)
IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, cardiovascular-drug, **combination** therapy, **tumor** eradication; combretastatin A-4 phosphate: **antineoplastic**-drug, cardiovascular-drug, **combination** therapy, **tumor** eradication
IT Methods & Equipment
radioimmunotherapy: **combination** therapy, iodine-131-labeled anticarcinoembryonic antigen antibody use, therapeutic method, **tumor** eradication
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
animal: animal model
Taxa Notes
Animals
RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 22 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:66602 BIOSIS
DOCUMENT NUMBER: PREV200100066602
TITLE: **Combining** drug-based vascular targeting therapies with radiation.
AUTHOR(S): Horsman, M. R. [Reprint author]
CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark
SOURCE: Radiotherapy and Oncology, (September, 2000) Vol. 56, No. Supplement 1, pp. S9-S10. print.
Meeting Info.: 19th Annual Meeting of the European Society for Therapeutic Radiology and Oncology. Istanbul, Turkey. September 19-23, 2000. European Society for Therapeutic Radiology and Oncology.
CODEN: RAONDT. ISSN: 0167-8140.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2001
Last Updated on STN: 12 Feb 2002
CC Pharmacology - General 22002
General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Methods and Techniques; Pharmacology; **Tumor** Biology
IT Diseases
tumor: **neoplastic** disease, treatment, treatment outcome
Neoplasms (MeSH)
IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic**-drug, vascular damaging agent; TNP-470: **antineoplastic**-drug, anti-angiogenesis inhibitor; angiostatin: **antineoplastic**-drug, anti-angiogenesis inhibitor; colchicine: **antineoplastic**-drug, vascular damaging agent; combrestatin A-4-disodium phosphate: **antineoplastic**-drug, vascular damaging agent; flavone acetic acid: **antineoplastic**-drug, vascular damaging agent
IT Methods & Equipment
drug-based vascular targeting therapy: **combination** therapy, efficacy, therapeutic method; radiation therapy: **combination** therapy, efficacy, radiologic method, therapeutic method
IT Miscellaneous Descriptors
neovasculature: growth prevention; **tumor** response; **tumor** vascular supply; Meeting Abstract
RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)
129298-91-5 (TNP-470)
86090-08-6 (angiostatin)
64-86-8 (colchicine)
87626-55-9 (flavone acetic acid)

L35 ANSWER 23 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1999:480131 BIOSIS
DOCUMENT NUMBER: PREV199900480131
TITLE: Enhancement of Antibody-directed Enzyme Prodrug Therapy in colorectal xenografts by an antivascular agent.
AUTHOR(S): Pedley, R. Barbara [Reprint author]; Sharma, Surinder K.; Boxer, Geoffrey M.; Boden, Robert; Stribbling, Stephen M.; Davies, Lawrence; Springer, Caroline J.; Begent, Richard H.J.
CORPORATE SOURCE: Department of Oncology, Royal Free and University College Medical School, University College London, Rowland Hill Street, Royal Free Campus, London, NW3 2PF, UK
SOURCE: Cancer Research, (Aug. 15, 1999) Vol. 59, No. 16, pp. 3998-4003. print.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Nov 1999
Last Updated on STN: 9 Nov 1999
AB The irregular nature of solid **tumor** vasculature produces a heterogeneous distribution of antibody-targeted therapies within the **tumor** mass, which frequently results in reduced therapeutic efficacy. We have, therefore, **combined** two complementary

therapies: Antibody-directed Enzyme Prodrug Therapy (ADEPT), which targets **tumor** cells, and an agent that selectively destroys **tumor** vasculature. A single i.p. dose (27.5 mg/kg) of the drug 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**), given to nude mice bearing the LS174T colorectal xenograft, destroyed all but a peripheral rim of **tumor** cells, without enhancing survival. The ADEPT system, in which a pretargeted enzyme activates a prodrug, consisted of the F(ab')2 fragment of anti-carcinoembryonic antigen antibody A5B7 conjugated to the bacterial enzyme carboxypeptidase G2 and the prodrug 4-((2-chloroethyl)(2-mesyloxyethyl)amino)benzoyl-L-glutamic acid, which was given i.p. in three doses of 500 mg/kg at 72, 84, and 96 h post-conjugate administration (25 units of carboxypeptidase G2). The antibody-enzyme conjugate could be selectively retained at approximately twice the control levels by administration of the antivascular agent at the time of optimal conjugate localization within the **tumor** (20 h post-conjugate administration), as demonstrated by gamma counting, phosphor plate image analysis, and active enzyme measurement. This resulted in significantly enhanced **tumor** growth inhibition in groups of six mice, compared to conventional ADEPT therapy, with no concomitant increase in systemic toxicity. In a separate experiment, aimed at trapping the prodrug within the **tumor**, a 16-fold increase over control values was produced (means, 44.8 versus 2.8 mug/g **tumor**) when **DMXAA** was given 4 h prior to 4-((2-chloroethyl)(2-mesyloxyethyl)amino)benzoyl-L-glutamic acid. The therapeutic window was small, with no significant enhancement of prodrug retention when **DMXAA** was given at either earlier or later time points. This correlated withthe time of vascular shut-down induced by the antivascular agent. We are currently investigating whether it is more advantageous to trap increased levels of conjugate or prodrug within the **tumor** for maximal enhancement of conventional ADEPT. These studies demonstrate that **combined** use of antibody-directed and antivascular therapies can significantly benefit the therapeutic outcome of either strategy alone.

CC Neoplasms - General 24002
Cytology - Human 02508
Biochemistry studies - General 10060
Pathology - Therapy 12512
Immunology - General and methods 34502
Metabolism - General metabolism and metabolic pathways 13002
Pharmacology - General 22002
General biology - Miscellaneous 00532

IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; **Tumor** Biology

IT Diseases
tumor: **neoplastic** disease, vasculature
Neoplasms (MeSH)

IT Chemicals & Biochemicals
anti-carcinoembryonic antigen antibody A5B7; carboxypeptidase G2; 4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-L-glutamic acid: prodrug; 5,6-**dimethylxanthenone**-4-acetic acid: antivascular agent

IT Methods & Equipment
antibody-directed enzyme prodrug therapy: therapeutic method

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
LS174T cell line: human colon adenocarcinoma cells

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: nude
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 9074-87-7 (carboxypeptidase G2)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 24 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1999:259464 BIOSIS
DOCUMENT NUMBER: PREV199900259464
TITLE: Thalidomide increases both intra-**tumoural** **tumour** necrosis factor-alpha production and anti-**tumour** activity in response to 5,6-**dimethylxanthenone**-4-acetic acid.
AUTHOR(S): Cao, Z.; Joseph, W. R.; Browne, W. L.; Mountjoy, K. G.; Palmer, B. D.; Baguley, B. C.; Ching, L.-M. [Reprint author]
CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland School of Medicine, Private Bag 92019, Auckland, New Zealand
SOURCE: British Journal of Cancer, (May, 1999) Vol. 80, No. 5-6, pp. 716-723. print.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1999
Last Updated on STN: 2 Jul 1999
AB 5,6-**Dimethylxanthenone**-4-acetic acid (**DMXAA**), synthesized in this laboratory and currently in phase I clinical trial, is a low molecular weight inducer of **tumour** necrosis factor-alpha (TNF-alpha). Administration of **DMXAA** to mice with established transplantable **tumours** elicits rapid vascular collapse selectively in the **tumour**, followed by extensive haemorrhagic necrosis mediated primarily through the production of TNF-alpha. In this report we have investigated the synthesis of TNF-alpha mRNA in hepatic, splenic and **tumour** tissue. Co-administration of thalidomide with **DMXAA** increased anti-**tumour** activity and increased intra-**tumoural** TNF-alpha production approximately tenfold over that obtained with **DMXAA** alone. Thalidomide increased splenic TNF-alpha production slightly but significantly decreased serum and hepatic levels of TNF-alpha induced with **DMXAA** . Lipopolysaccharide (LPS) induced 300-fold higher serum TNF-alpha than did **DMXAA** at the maximum tolerated dose, but induced similar amounts of TNF-alpha in spleen, liver and **tumour**. Splenic TNF-alpha activity induced with LPS was slightly increased with thalidomide, but serum and liver TNF-alpha levels were suppressed. Thalidomide did not increase intra-**tumoural** TNF-alpha production induced with LPS, in sharp contrast to that obtained with **DMXAA**. While thalidomide improved the anti-**tumour** response to **DMXAA**, it had no effect on the anti-**tumour** action of LPS that did not induce a significant growth delay or cures against the Colon 38 **tumour**. The increase in the anti-**tumour** action by

thalidomide in **combination** with **DMXAA** corresponded to an increase in intra-**tumoural** TNF-alpha production. Co-administration of thalidomide may represent a novel approach to improving selective intra-**tumoural** TNF-alpha production and anti-**tumour** efficacy of **DMXAA.**

CC Neoplasms - Therapeutic agents and therapy 24008
Metabolism - Carbohydrates 13004
Metabolism - Proteins, peptides and amino acids 13012
Endocrine - General 17002
Neoplasms - Biochemistry 24006
Pharmacology - Digestive system 22014
Digestive system - Pathology 14006
Biochemistry studies - General 10060
Pharmacology - Drug metabolism and metabolic stimulators 22003
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Pathology - Therapy 12512

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Diseases
colon 38 **tumor**: digestive system disease, **neoplastic** disease, drug treatment

IT Chemicals & Biochemicals
thalidomide: **antineoplastic**-drug, **combination** therapy; **tumor** necrosis factor-alpha: drug-induced **intratumoral** production increase; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, thalidomide-induced **antitumor** activity increase, **combination** therapy

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C57Bl/6 mouse: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 50-35-1 (thalidomide)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

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ACCESSION NUMBER: 1999:310629 BIOSIS
DOCUMENT NUMBER: PREV199900310629
TITLE: Inhibition of DT-diaphorase (NAD(P)H:Quinone oxidoreductase, EC 1.6.99.2) by 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) and flavone-8-acetic acid (FAA): Implications for bioreductive drug development.
AUTHOR(S): Phillips, Roger M. [Reprint author]
CORPORATE SOURCE: Clinical Oncology Unit, University of Bradford, Bradford, BD7 1DP, UK
SOURCE: Biochemical Pharmacology, (July 15, 1999) Vol. 58, No. 2, pp. 303-310. print.
CODEN: BCPCA6. ISSN: 0006-2952.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Aug 1999
Last Updated on STN: 30 Sep 1999

AB The **tumour** blood flow inhibitors 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**) and flavone-8-acetic acid (FAA) have been shown to potentiate the **antitumour** activity of several bioreductive drugs in vivo. Whilst the induction of hypoxia as a result of blood flow inhibition is presumed to be responsible for enhancing the activity of bioreductive drugs, no studies have examined potential interactions between **DMXAA** or FAA and enzymes involved in bioreductive drug activation. Both FAA and **DMXAA** are competitive inhibitors of the enzyme DT-diaphorase (NAD(P)H:Quinone oxidoreductase EC 1.6.99.2) with respect to NADH, with Ki values of 75 and 20 muM, respectively. Cytochromes P450 reductase and b5 reductase activities are not significantly inhibited by FAA, whereas **DMXAA** partially inhibits cytochrome b5 reductase activity. The cytotoxicity of the indoloquinone EO9 (3-hydroxymethyl-5-aziridinyl-1-methyl-2-(1H-indole-4,7-dione) prop-beta-en-alpha-ol) against DLD-1 (IC50 = 0.32 +- 0.08 muM) was significantly reduced when **combinations** of EO9 and FAA (IC50 = 12.26 +- 5.43 muM) or **DMXAA** (IC50 > 40 muM) were used. In the case of menadione (which is detoxified by DT-diaphorase), **combinations** of menadione with FAA or **DMXAA** were more toxic (IC50 = 7.46 +- 2.22 and 9.46 +- 1.70 muM, respectively) than menadione alone (IC50 = 22.02 +- 1.59 muM). Neither **DMXAA** nor FAA potentiated the activity of tirapazamine in vitro. These results suggest that the use of **DMXAA** and FAA to potentiate the activity of bioreductive drugs where DT-diaphorase plays a central role in either activation or detoxification may be inappropriate. The fact that FAA in particular does not inhibit other key enzymes involved in bioreductive activation suggests that it may be useful in terms of identifying DT-diaphorase-activated prodrugs.

CC Pharmacology - General 22002
Cytology - Human 02508
Biochemistry studies - General 10060
Neoplasms - Therapeutic agents and therapy 24008
Enzymes - Physiological studies 10808

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

IT Chemicals & Biochemicals
bioreductive drug: development; cytochrome b-5 reductase: inhibition; cytochrome P450 reductase: inhibition; flavone-8-acetic acid: **antineoplastic** agent, **tumor** blood flow inhibitor agent, enzyme inhibitor; DT-diaphorase [EC 1.6.99.2]: inhibition; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** agent, **tumor** blood flow inhibitor agent, enzyme inhibitor

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
DLD-1 cell line
H460 cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 9032-25-1 (cytochrome b-5 reductase)
9039-06-9 (cytochrome P450 reductase)
87626-55-9 (flavone-8-acetic acid)
9032-20-6 (DT-diaphorase)
9032-20-6 (EC 1.6.99.2)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

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ACCESSION NUMBER: 1999:441521 BIOSIS
DOCUMENT NUMBER: PREV199900441521
TITLE: Improving conventional **cancer** therapy by targeting **tumour** vasculature.
AUTHOR(S): Horsman, M. R. [Reprint author]; Murata, R. [Reprint author]; Overgaard, J. [Reprint author]
CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, DK-8000, Denmark
SOURCE: British Journal of Cancer, (July, 1999) Vol. 80, No. SUPPL. 2, pp. 90. print.
Meeting Info.: Joint Meeting of the British Association for Cancer Research, the British Oncological Association, the Association of Cancer Physicians and the Royal College of Radiologists. Edinburgh, Scotland, UK. July 11-14, 1999.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999

CC Pharmacology - General 22002
Pathology - Therapy 12512
Cardiovascular system - General and methods 14501
Neoplasms - General 24002
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
cisplatin: **antineoplastic**-drug, **combination** therapy; combretastatin A-4 disodium phosphate: **antineoplastic** -drug, vascular damaging agent; flavone acetic acid: **antineoplastic**-drug, vascular damaging agent; vascular targeting drugs; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic**-drug, vascular damaging agent

IT Methods & Equipment
cancer therapy: therapeutic method

IT Miscellaneous Descriptors
tumor vasculature; Meeting Abstract; Meeting Poster

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model
C3H cell line: murine mammary carcinoma cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 15663-27-1 (cisplatin)
168555-66-6 (combretastatin A-4 disodium phosphate)
87626-55-9 (flavone acetic acid)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)
7558-79-4 (DISODIUM PHOSPHATE)
82855-09-2 (COMBRETASTATIN)

L35 ANSWER 27 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1999:439578 BIOSIS

DOCUMENT NUMBER: PREV199900439578
TITLE: Potentiation of chemotherapy by vascular targeting agents.
AUTHOR(S): Siemann, D. W. [Reprint author]; Taylor, D. [Reprint author]; Leppler, S. E. [Reprint author]
CORPORATE SOURCE: Department of Radiation Oncology and Shands Cancer Center, University of Florida, Gainesville, FL, 32610, USA
SOURCE: British Journal of Cancer, (July, 1999) Vol. 80, No. SUPPL. 2, pp. 90. print.
Meeting Info.: Joint Meeting of the British Association for Cancer Research, the British Oncological Association, the Association of Cancer Physicians and the Royal College of Radiologists. Edinburgh, Scotland, UK. July 11-14, 1999.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999

CC Pharmacology - General 22002
Pathology - Therapy 12512
Cardiovascular system - General and methods 14501
Neoplasms - General 24002
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
cisplatin: **antineoplastic**-drug, **combination** therapy; combretastatin A-4 disodium phosphate: **antineoplastic**-drug, **combination** therapy, vascular targeting agent; cyclophosphamide: **antineoplastic**-drug, **combination** therapy; **dimethylxanthenone** acetic acid: **antineoplastic**-drug, vascular targeting agent, **combination** therapy; vascular targeting agents

IT Methods & Equipment
chemotherapy: potentiation, therapeutic method

IT Miscellaneous Descriptors
tumor vascularization; Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
SKBR3 cell line: human breast **cancer** cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

ORGN Classifier
Rodentia 86265
Super Taxa
Mammalia; Vertebrata; Chordata; Animalia
Organism Name

KHT cell line: rodent sarcoma cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 15663-27-1 (cisplatin)
168555-66-6 (combretastatin A-4 disodium phosphate)
50-18-0 (cyclophosphamide)
64-19-7 (ACETIC ACID)
7558-79-4 (DISODIUM PHOSPHATE)
82855-09-2 (COMBRETASTATIN)

L35 ANSWER 28 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1999:93338 BIOSIS
DOCUMENT NUMBER: PREV199900093338
TITLE: Suppression of serum **tumour** necrosis factor-alpha by thalidomide does not lead to reversal of **tumour** vascular collapse and anti-**tumour** activity of 5,6-**dimethylxanthenone**-4-acetic acid.
AUTHOR(S): Browne, William L.; Wilson, William R.; Baguley, Bruce C.; Ching, Lai-Ming [Reprint author]
CORPORATE SOURCE: Auckland Cancer Soc. Res. Cent., Univ. Auckland Sch. Med., Private Bag 92019, Auckland, New Zealand
SOURCE: Anticancer Research, (Nov.-Dec., 1998) Vol. 18, No. 6A, pp. 4409-4414. print.
CODEN: ANTRD4. ISSN: 0250-7005.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Mar 1999
Last Updated on STN: 1 Mar 1999
AB The **antitumour** agent 5,6-**dimethytlxanthenone**-4-acetic acid (**DMXAA**), developed in this laboratory as a potent analogue of flavone acetic acid (FAA), has a novel **antitumour** action involving both immune and vascular components. **DMXAA** induces the synthesis of **tumour** necrosis factor-alpha (TNF) and it has been hypothesized that this mediates its selective reduction of **tumour** blood flow and consequent induction of **tumour** necrosis. Unexpectedly, the drug thalidomide, while reducing the serum TNF response to **DMXAA**, potentiates its **antitumour** effect. We have investigated this in the MDAH-MCa-4 mammary carcinoma model, comparing it to previous data with the Colon 38 adenocarcinoma. We have related **DMXAA**-induced blood flow changes in the MCa-4 **tumour** to **tumour** growth delay, serum TNF and extractable TNF from **tumour** tissue. We have also compared the effect of thalidomide (387 mumol/kg) on **DMXAA** (80 mumol/kg) with that of a monoclonal anti-TNF antibody (50 mug/mouse). We find that **tumour** blood flow reduction is strongly correlated with **tumour** growth delay. Co-administration of anti-TNF antibody abolishes serum TNF levels and slightly reduces the **antitumour** effects of **DMXAA.** While **tumour** growth delay is not correlated with serum induced TNF levels, it is related to **tumour** TNF levels. We conclude that while the data are consistent with TNF being the principal mediator of the action of **DMXAA**, serum TNF levels do not reflect the **antitumour** response.
CC Neoplasms - Therapeutic agents and therapy 24008
Biochemistry studies - Proteins, peptides and amino acids 10064
Metabolism - Carbohydrates 13004
Metabolism - Proteins, peptides and amino acids 13012
Cardiovascular system - Physiology and biochemistry 14504
Cardiovascular system - Blood vessel pathology 14508

Reproductive system - Pathology 16506
Endocrine - General 17002
Pharmacology - Cardiovascular system 22010
Pharmacology - Reproductive system and implantation studies 22028
Neoplasms - Biochemistry 24006
Biochemistry studies - General 10060
Biochemistry studies - Carbohydrates 10068
Movement 12100
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Laboratory animals - General 28002

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Diseases
MCa-4 mammary carcinoma: **neoplastic** disease, reproductive system disease/female, drug-induced blood flow changes, drug-induced growth delay

IT Chemicals & Biochemicals
thalidomide: **antineoplastic**-drug, **combination** therapy; **tumor** necrosis factor-alpha: serum level, thalidomide-induced suppression, **tumor** tissue level; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, cardiovascular-drug, **combination** therapy

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C3H/HeN mouse: animal model, female
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 50-35-1 (thalidomide)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 29 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 3

ACCESSION NUMBER: 1999:67192 BIOSIS
DOCUMENT NUMBER: PREV199900067192
TITLE: Enhancement of **tumor** radiation response by the antivascular agent 5,6-**dimethylxanthenone** -4-acetic acid.
AUTHOR(S): Wilson, William R. [Reprint author]; Li, Alan E.; Cowan, David S. M.; Siim, Bronwyn G.
CORPORATE SOURCE: Section Oncol., Dep. Pathol., Univ. Auckland, Private Bag 92019, Auckland, New Zealand
SOURCE: International Journal of Radiation Oncology Biology Physics, (Nov. 1, 1998) Vol. 42, No. 4, pp. 905-908. print. CODEN: IOBPD3. ISSN: 0360-3016.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Feb 1999
Last Updated on STN: 16 Feb 1999

AB Purpose: 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) selectively damages **tumor** vasculature and is currently in clinical trial as an **antitumor** agent. Its ability to induce synthesis of **tumor** necrosis factor (TNF), and its apparent selectivity for poorly-perfused regions in **tumors**, suggests it possible use in **combination** with radiotherapy. This

investigation examines activity of **DMXAA** as a radiation modifier using two murine **tumors.** Methods and Materials: **Tumor** growth delay was evaluated using i.m. RIF-1 and MDAH-MCa-4 **tumors** irradiated in anaesthetized, restrained mice (cobalt-60) using single dose or multiple fractions (8 X 2.5 Gy over 4 days) with **DMXAA** administered ip. at various times in relation to irradiation. Results: Administration of **DMXAA** (80 mumol/kg, i.p.) immediately after radiation resulted in a large increase in **tumor** growth delay, giving a radiation dose modifying factor of 2.3 for RIF-1 and 3.9 for MDAH-MCa-4. The **combination** was less active when radiation was given 1-4 h after **DMXAA**, but was highly active 12-48 h after **DMXAA.** At the latter times, clamping the **tumor** blood supply caused a large increase in radioresistance. These studies suggest that cells surviving **DMXAA** are hypoxic for only a short period. **DMXAA** increased overall growth delay when administered daily during fractionated irradiation, giving an approximately additive response. Conclusions: The marked synergy between **DMXAA** and single dose ionizing radiation may reflect the complementarity of these agents at the microregional level, with **DMXAA** preferentially killing hypoxic cells in poorly perfused regions. Despite additional hypoxia shortly after **DMXAA** treatment, surviving cells appear to reoxygenate quickly which makes it feasible to use **DMXAA** before and during fractionated radiotherapy. The **combination** of fractionated radiation and **DMXAA** appears to be less effective than for single dose radiation (possibly because of the smaller contribution of hypoxia under these conditions), but may be therapeutically useful.

CC Neoplasms - Therapeutic agents and therapy 24008
Radiation biology - Radiation and isotope techniques 06504
Radiation biology - Radiation effects and protective measures 06506
Cardiovascular system - Physiology and biochemistry 14504
Reproductive system - Pathology 16506
Bones, joints, fasciae, connective and adipose tissue - Pathology 18006
Pharmacology - Cardiovascular system 22010
Pharmacology - Connective tissue, bone and collagen-acting drugs 22012
Pharmacology - Reproductive system and implantation studies 22028
Biochemistry studies - General 10060
Pathology - Therapy 12512
Laboratory animals - General 28002

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Diseases
MDAH-MCa-4 mammary **tumor**: reproductive system disease/female, **neoplastic** disease, chemoradiotherapy

IT Diseases
RIF-1 fibrosarcoma: **neoplastic** disease, connective tissue disease, chemoradiotherapy

IT Chemicals & Biochemicals
5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, radiosensitizer-drug, antivascular agent

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **117570-53-3** (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 30 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 4

ACCESSION NUMBER: 1998:436633 BIOSIS
DOCUMENT NUMBER: PREV199800436633
TITLE: Enhancement of the anti-**tumour** effects of the antivascular agent 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**) by **combination** with 5-hydroxytryptamine and bioreductive drugs.
AUTHOR(S): Lash, C. J.; Li, A. E.; Rutland, M.; Baguley, B. C.; Zwi, L. J.; Wilson, W. R. [Reprint author]
CORPORATE SOURCE: Sect. Oncology, Dep. Pathol., Univ. Auckland, Private Bag 92019, Auckland, New Zealand
SOURCE: British Journal of Cancer, (Aug., 1998) Vol. 78, No. 4, pp. 439-445. print.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 1998
Last Updated on STN: 5 Nov 1998

AB The **tumour** blood flow inhibitor 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**) causes dramatic haemorrhagic necrosis in murine **tumours**, but activity is seen only at doses close to the toxic limit. This study investigates two approaches for increasing the therapeutic ratio of **DMXAA.** The first approach **combines** **DMXAA** with a second **tumour** blood flow inhibitor, 5-hydroxytryptamine (5-HT). Co-administration of 5-HT (700 mumol kg-1) to C3H mice caused marked enhancement of **DMXAA** effects against MDAH-MCa-4 **tumours**, with dose-modifying factors (DMFs) of >3 for blood flow inhibition (at 4 h), 2.3 for necrosis (at 12 h) and 2.0 for growth delay, without compromising the maximum tolerated dose of **DMXAA** (90 mumol kg-1). The data are consistent with ischemic injury to the **tumour** being the major mechanism of **antitumor** activity. The second approach **combines** **DMXAA** (+- 5-HT) with hypoxia-selective bioreductive drugs. Anti-**tumour** activity of all three bioreductive drugs tested (tirapazamine, CI-1010, SN 23816) was strongly potentiated by **DMXAA**, suggesting that there is a population of reversibly hypoxic **tumour** cells after **DMXAA** treatment. Co-administration of 5-HT further potentiated anti-**tumour** activity, but also increased host toxicity of tirapazamine and CI-1010 so that little therapeutic benefit was achieved. In contrast, the host toxicity of the dinitrobenzamide mustard SN 23816 was only slightly increased by **DMXAA**/5-HT, whereas the **tumour** growth delay at the maximum tolerated dose of SN 23816 was increased from 3.5 to 26.5 days. This study demonstrates that 5-HT and/or bioreductive drugs can improve the therapeutic activity of **DMXAA** in mice, and that with SN 23816 both approaches can be used together to provide considerably enhanced anti-**tumour** activity.

CC Neoplasms - Therapeutic agents and therapy 24008
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Cardiovascular system - Physiology and biochemistry 14504
Pharmacology - Cardiovascular system 22010
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
bioreductive drugs: **antitumor** effect; 5-hydroxytryptamine:

antitumor effect, blood flow inhibitor; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic** -drug, antivascular agent, **tumor** blood flow inhibitor, maximum tolerated dose
IT Miscellaneous Descriptors
blood flow inhibition; dose-modifying factor; necrosis
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
murine
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 50-67-9 (5-hydroxytryptamine)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

L35 ANSWER 31 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 5
ACCESSION NUMBER: 1998:394707 BIOSIS
DOCUMENT NUMBER: PREV199800394707
TITLE: Interaction of thalidomide, phthalimide analogues of thalidomide and pentoxylline with the anti-**tumour** agent 5,6-**dimethylxanthenone**-4-acetic acid: Concomitant reduction of serum **tumour** necrosis factor-alpha and enhancement of anti-**tumour** activity.
AUTHOR(S): Ching, L.-M. [Reprint author]; Browne, W. L.; Tchernegovsky, R.; Gregory, T.; Baguley, B. C.; Palmer, B. D.
CORPORATE SOURCE: Auckland Cancer Society Res. Centre, Univ. Auckland Sch. Med., Private Bag 92019, Auckland, New Zealand
SOURCE: British Journal of Cancer, (Aug., 1998) Vol. 78, No. 3, pp. 336-343. print.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Sep 1998
Last Updated on STN: 21 Oct 1998
AB **DMXAA** (5.6-**dimethylxanthenone**-4-acetic acid), a novel anti-**tumour** agent currently undergoing clinical evaluation, appears to mediate its anti-**tumour** effects through immune modulation and the production of the cytokine **tumour** necrosis factor-alpha (TNF). Our previous studies have shown that thalidomide, a potent inhibitor of TNF biosynthesis that has numerous biological effects, including inhibition of **tumour** angiogenesis, unexpectedly augments the anti-**tumour** response in mice to **DMXAA.** We show here that thalidomide (100 mg kg-1) has no effect when administered with inactive doses of **DMXAA**, and that it must be given simultaneously With an active dose of **DMXAA** to have its maximum potentiating effect on the growth of the murine Colon 38 adenocarcinoma. To address the issue of whether inhibition of serum TNF production is important for potentiation of anti-**tumour** activity, we have tested three potent analogues of thalidomide. All three analogues, when co-administered with **DMXAA** to mice at doses lower than those used with thalidomide, inhibited TNF production and were effective in potentiating the anti-**tumour** activity of **DMXAA** against transplanted Colon 38 **tumours.** One of the analogues, N-phenethyltetrafluorophthalimide, was 1 000-fold more potent

than thalidomide and at a dose of 0.1 mg kg-1 in **combination** with **DMXAA** (30 mg kg-1) cured 100% of mice, compared with 67% for the group treated with **DMXAA** alone. We also tested pentoxifylline and found it to suppress TNF production in response to **DMXAA** and to potentiate the anti-**tumour** effect of **DMXAA**. The results are compatible with the hypothesis that pharmacological reduction of serum TNF levels might benefit the anti-**tumour** effects of **DMXAA** and suggest new strategies for therapy using this agent.

CC Neoplasms - Therapeutic agents and therapy 24008
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Carbohydrates 13004
Metabolism - Proteins, peptides and amino acids 13012
Digestive system - Pathology 14006
Endocrine - General 17002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Digestive system 22014
Neoplasms - Biochemistry 24006
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Laboratory animals - General 28002

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Diseases
colon 38 **tumor**: digestive system disease, **neoplastic** disease, drug treatment

IT Chemicals & Biochemicals
thalidomide: **antineoplastic**-drug, **antitumor** agent interaction, phthalimide analogues, **combination** therapy; **tumor** necrosis factor-alpha: drug-induced serum level reduction; 5,6-**dimethylxanthenone**-4-acetic acid: **antineoplastic**-drug, **combination** therapy, thalidomide interaction, phthalimide analogue interaction

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
BDF-1 mouse: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 50-35-1 (thalidomide)
117570-53-3 (5,6-**dimethylxanthenone**-4-acetic acid)

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ACCESSION NUMBER: 1998:35808 BIOSIS
DOCUMENT NUMBER: PREV199800035808
TITLE: Nitro reduction as an electronic switch for bioreductive drug activation.
AUTHOR(S): Siim, Bronwyn G. [Reprint author]; Denny, William A.; Wilson, William R.
CORPORATE SOURCE: Section Oncol., Dep. Pathol., Univ. Auckland, Private Bag 92019, Auckland, New Zealand
SOURCE: Oncology Research, (1997) Vol. 9, No. 6-7, pp. 357-369. print.

CODEN: ONREE8. ISSN: 0965-0407.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jan 1998
Last Updated on STN: 24 Feb 1998

AB It is well known that the reduction of aromatic nitro groups can give rise to toxic species, and that net nitro reduction by one-electron reductases can usually be inhibited by oxygen. There has been much interest in utilizing this biotransformation to activate drugs in hypoxic regions of **tumors**, but no clinically useful compound has yet resulted. Nitroreductive activation of prodrugs by oxygen-insensitive (and oxygen-sensitive) reductases is also of current interest because of new methods for introducing specific nitroreductases into **tumors** (e.g., as antibody-enzyme conjugates or by gene therapy). In most of the compounds investigated previously, cytotoxicity appears to be due to reactive nitroso or hydroxylamine reduction products arising from the nitro group itself. It is argued that there is greater scope for designing potent and selective nitro compounds by using the nitro group as an electronic switch to activate a latent reactive moiety elsewhere in the molecule. Examples of this approach include the nitro(hetero)aromatic mustards (e.g., SN 23816, NSC 646394) in which the nitro group controls the reactivity of a nitrogen mustard to which it is directly conjugated, and the nitro(hetero)aromatic methylquaternary (NMQ) mustards (e.g., SN 25341, NSC 658926) in which reduction of the nitro group triggers fragmentation of the molecule to release a reactive aliphatic nitrogen mustard. Many of these compounds show very high selectivity for hypoxic cells in culture. Some are also active against hypoxic cells in **tumors**, and provide large **tumor** growth delays when **combined** with **tumor** blood flow inhibitors such as 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**). These prodrug designs also have potential for releasing effectors other than nitrogen mustards, which opens up many possibilities for use of nitro compounds as **tumor**-selective prodrugs.

CC Neoplasms - Therapeutic agents and therapy 24008
Cytology - Animal 02506
Reproductive system - Pathology 16506
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Reproductive system and implantation studies 22028
Neoplasms - Neoplastic cell lines 24005
Biochemistry studies - General 10060
Biophysics - Molecular properties and macromolecules 10506
Pathology - Therapy 12512
Tissue culture, apparatus, methods and media 32500

IT Major Concepts
Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
nitro(hetero) aromatic methylquaternary mustards: **antineoplastic**-drug, NSC-658926, SN-25341, nitro reduction, bioreductive activation; nitro(hetero)aromatic mustards: **antineoplastic**-drug, NSC-646394, SN-23816, nitro reduction, bioreductive activation

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
EMT-6: drug treatment, in-vitro model system, mouse mammary **tumor** cell line

Walker S: drug treatment, rat carcinoma cell line, in-vitro model system
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

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ACCESSION NUMBER: 1997:77305 BIOSIS
DOCUMENT NUMBER: PREV199799384008
TITLE: Chemotherapy with **DMXAA** (5,6-**dimethylxanthenone**-4-acetic acid) in **combination** with CI-1010 (1H-imidazole-1-ethanol,alpha-(((2-bromoethyl)amino)methyl)-2-nitro-, mono-hydrobromide (R isomer)) against advanced stage murine colon carcinoma 26.
AUTHOR(S): Vincent, Patrick W. [Reprint author]; Roberts, Billy J.; Elliott, William L.; Leopold, Wilbur R.
CORPORATE SOURCE: Parke-Davis Pharmaceutical Res., 2800 Plymouth Rd., Ann Arbor, MI 48105, USA
SOURCE: Oncology Reports, (1997) Vol. 4, No. 1, pp. 143-147. ISSN: 1021-335X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1997
Last Updated on STN: 2 Apr 1997

AB Because an enhanced therapeutic gain might be expected with co-administration of a hypoxic cell selective cytotoxin and a compound that induces hemorrhagic necrosis in **tumors**, the **combination** of CI-1010 (a potent bioreductive hypoxia selective cytotoxin) and 5,6-**dimethylxanthenone**-4-acetic acid (**DMXAA**) has been evaluated against advanced stage (gt 150 mg) murine colon carcinoma 26 (C26). CI-1010 and **DMXAA** were administered intraperitoneally over a range of toxic to ineffective doses as single agents and in **combination** to adult BALB/c times DBA/2 F1 hybrid mice bearing s.c. implants of C26. Both CI-1010 and **DMXAA** were ineffective as single agents, but regimens **combining** these two agents were highly active. The administration of **DMXAA** at 20 mg/kg/inj on days 9, 13, and 17 and CI-1010 at 65 mg/kg/inj on days 9-17 resulted in 60% of the animals **tumor** free on day 92 of the study. The remaining animals that were not **tumor** free survivors achieved a delay in **tumor** growth of 22.4 days. However, this treatment regimen was also considered toxic resulting in 2/10 treatment related deaths. Modification of the CI-1010 treatment schedule to intermittent delivery 24 h after each scheduled dose of **DMXAA** reduced treatment related toxicity while retaining efficacy. On this schedule the **combination** of CI-1010 (95 mg/kg/inj) given 24 h after **DMXAA** (20 mg/kg/inj) on days 9, 13, and 17 resulted in 60% of the treated animals **tumor** free on day 98 of the study. Treatment failures experienced a **tumor** growth delay of 11.6 days. **Combination** chemotherapy with CI-1010 and **DMXAA** was ineffective when **DMXAA** was administered 1 h prior to CI-1010, simultaneously with CI-1010, or 1 h after the administration of CI-1010. These results suggest that an enhanced therapeutic interaction between CI-1010 and **DMXAA** is achievable in vivo and that this interaction requires the development of substantial **DMXAA** induced **tumor** hypoxia prior to administration of CI-1010.

CC Digestive system - General and methods 14001
Pharmacology - General 22002
Neoplasms - General 24002

IT Major Concepts
Digestive System (Ingestion and Assimilation); Pharmacology; **Tumor** Biology
IT Chemicals & Biochemicals
ACETIC ACID
IT Miscellaneous Descriptors
ADULT; **ANTINEOPLASTIC**-DRUG; BALB/C X DBA/2; CI-1010; COLON CARCINOMA; **COMBINATION** THERAPY; C26 CELL LINE; C26 MODEL; DIGESTIVE SYSTEM DISEASE; **DMXAA**; **DMXAA**-CI-1010; MURINE COLON CARCINOMA CELLS; **NEOPLASTIC** DISEASE; PHARMACOLOGY; R ISOMER; THERAPEUTIC METHOD; **TUMOR** BIOLOGY; **TUMOR** GROWTH DELAY; **TUMOR** HYPOXIA; 1H-IMIDAZOLE-1-ETHANOL,ALPHA(((2-BROMOETHYL)AMINO)METHYL)-2-NITRO, MONO-HYDROBROMIDE; 5,6-**DIMETHYLXANTHENONE**-4-ACETIC ACID
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 64-19-7 (ACETIC ACID)

L35 ANSWER 34 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1996:368522 BIOSIS
DOCUMENT NUMBER: PREV199699090878
TITLE: Ablation of colorectal xenografts with **combined** radioimmunotherapy and **tumor** blood flow-modifying agents.
AUTHOR(S): Pedley, R. Barbara [Reprint author]; Boden, Joan A.; Boden, Robert; Boxer, Geoffrey M.; Flynn, Aiden A.; Keep, Patricia A.; Begent, Richard H. J.
CORPORATE SOURCE: Dep. Clinical Oncol., Royal Free Hosp. Sch. Med., Rowland Hill St., London NW3 2PF, UK
SOURCE: Cancer Research, (1996) Vol. 56, No. 14, pp. 3293-3300. CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 1996
Last Updated on STN: 26 Sep 1996
AB Radioimmunotherapy (RIT) does not readily eradicate common solid **tumors** and therefore requires augmentation by complementary therapies that do not increase normal tissue damage. We have examined the efficacy of RIT **combined** with 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**), a drug which induces immunomodulation and cytokine production and preferentially reduces **tumor** blood flow, using a colorectal xenograft model in nude mice. Although an optimal i.p. dose (27.5 mg/kg) of drug alone induced massive hemorrhagic necrosis of all but a thin peripheral rim of viable **tumor** cells, survival was unaffected. However, when **combined** with i.v. 18.5 MBq 131I-labeled anti-carcinoembryonic antigen IgG, **DMXAA** significantly potentiated the RIT without increased toxicity, with five of six mice showing complete cures. Scheduling was critical because the antibody must be allowed to reach maximum **tumor** accumulation before initiation of drug-induced blood flow inhibition. Subsequently, the antibody was retained preferentially in the **tumor**, reaching approximately twice control levels by 5 days after drug delivery. In

combined studies, the drug had a narrow therapeutic window, 30 mg/kg being toxic to two of six mice, whereas 20 mg/kg were ineffective. However, the addition of a second vasoactive agent, serotonin, to RIT plus 20 mg/kg **DMXAA** enhanced therapy without increasing systemic toxicity. **Tumor** histology and phosphor image plate analysis reflected these results. When given without RIT, the two drugs **combined**, although not alone, also significantly inhibited **tumor** growth. Drug-induced **tumor** necrosis and **tumor** retention of radioantibody may both contribute to the enhanced RIT produced by this **combined** complementary therapy.

CC Cytology - Human 02508
Radiation biology - Radiation and isotope techniques 06504
Radiation biology - Radiation effects and protective measures 06506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Anatomy and Histology - Regeneration and transplantation 11107
Movement 12100
Pathology - Necrosis 12510
Pathology - Therapy 12512
Metabolism - Carbohydrates 13004
Metabolism - Proteins, peptides and amino acids 13012
Digestive system - Pathology 14006
Cardiovascular system - General and methods 14501
Cardiovascular system - Blood vessel pathology 14508
Blood - Blood and lymph studies 15002
Endocrine - General 17002
Endocrine - Neuroendocrinology 17020
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Cardiovascular system 22010
Pharmacology - Digestive system 22014
Pharmacology - Endocrine system 22016
Pharmacology - Immunological processes and allergy 22018
Routes of immunization, infection and therapy 22100
Toxicology - Pharmacology 22504
Neoplasms - Immunology 24003
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Therapeutic agents and therapy 24008
Development and Embryology - General and descriptive 25502
Tissue culture, apparatus, methods and media 32500
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Clinical Endocrinology (Human Medicine, Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology; Physiology; Radiology (Medical Sciences)

IT Chemicals & Biochemicals
ACETIC ACID; SEROTONIN

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CARDIOVASCULAR-DRUG; HEMORRHAGIC NECROSIS; HORMONE-DRUG; IMMUNOLOGIC-DRUG; SEROTONIN; 5,6-**DIMETHYLXANTHENONE**-4-ACETIC ACID

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 64-19-7 (ACETIC ACID)
50-67-9 (SEROTONIN)

L35 ANSWER 35 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1996:415760 BIOSIS
DOCUMENT NUMBER: PREV199699138116
TITLE: Changes in coagulation and permeability properties of human endothelial cells in vitro induced by TNF-alpha or 5,6 MeXAA.
AUTHOR(S): Watts, M. E. [Reprint author]; Arnold, S.; Chaplin, D. J.
CORPORATE SOURCE: Tumour Microcirculation Group, Gray Lab. Cancer Res. Trust, P.O. Box 100, Mount Vernon Hosp., Northwood, Middlesex HA6 2JR, UK
SOURCE: British Journal of Cancer, (1996) Vol. 74, No. SUPPL. 27, pp. S164-S167.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Sep 1996
Last Updated on STN: 10 Sep 1996

AB 5,6 **dimethyl xanthenone** acetic acid (5,6 MeXAA), an analogue of flavone acetic acid (FAA), has been shown to be more active against murine turnouts than FAA. As both drugs have a vascular component in their mechanism of action similar to that observed for TNF-alpha, we have studied the effects of 5,6 MeXAA alone and in **combination** with TNF-alpha on endothelial function in vitro. The changes induced by the drugs on procoagulant activity and permeability were determined under **tumour**-simulated conditions of low oxygen tension and the presence of **tumour**-secreted factors. Procoagulant activity was assayed by measuring the time taken for human umbilical vein endothelial cells (HUVECs) to clot normal human plasma, increased activity resulting in reduced clotting times. HUVECs incubated under aerobic conditions were more sensitive to TNF-alpha than cells incubated at ltoreq 0.2% oxygen. Culture medium conditioned by the human breast adenocarcinoma cell line MDA-MB-231 strongly upregulated procoagulant activity under both aerobic and hypoxic conditions; clotting times were further reduced by TNF-alpha. Both 5,6 MeXAA and FAA potentiated the effect of TNF-alpha on normal hypoxic endothelial cells; however, under all other conditions, neither drug in **combination** with TNF-alpha upregulated clotting activity. The presence of **tumour**-secreted factors had a far greater effect on upregulating procoagulant activity than did oxygen tension. In contrast to procoagulant activity, permeability was insensitive to TNF-alpha and low concentrations of 5,6 MeXAA also caused no change in permeability.

CC Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Biophysics - Membrane phenomena 10508
Cardiovascular system - Physiology and biochemistry 14504

Blood - Blood and lymph studies 15002
Reproductive system - Pathology 16506
Endocrine - General 17002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Blood and hematopoietic agents 22008
Pharmacology - Cardiovascular system 22010
Pharmacology - Endocrine system 22016
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Reproductive system and implantation studies 22028
Neoplasms - Immunology 24003
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Therapeutic agents and therapy 24008
Development and Embryology - General and descriptive 25502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cardiovascular System (Transport and Circulation); Cell Biology; Clinical Endocrinology (Human Medicine, Medical Sciences); Development; Endocrine System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Oncology (Human Medicine, Medical Sciences); Pharmacology; Reproductive System (Reproduction)

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CARDIOVASCULAR-DRUG; FLAVONEACETIC ACID; HORMONE-DRUG; IN-VITRO; MDA-MB-231 BREAST **CANCER** CELLS; MOUSE **TUMOR**; **TUMOR** NECROSIS FACTOR-ALPHA; UMBILICAL VEIN CELLS; 5,6-**DIMETHYLXANTHENONEACETIC** ACID

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hominidae
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

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ACCESSION NUMBER: 1996:415741 BIOSIS
DOCUMENT NUMBER: PREV199699138097
TITLE: Tertiary amine N-oxides as bioreductive drugs: DACA N-oxide, nitracrine N-oxide and AQ4N.
AUTHOR(S): Wilson, W. R. [Reprint author]; Denny, W. A.; Pullen, S. M.; Thompson, K. M.; Li, A. E.; Patterson, L. H.; Lee, H. H.
CORPORATE SOURCE: Sect. Oncol., Dep. Pathol., The Univ. Auckland, Private Bag 92019, Auckland, New Zealand
SOURCE: British Journal of Cancer, (1996) Vol. 74, No. SUPPL. 27, pp. S43-S47.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English

ENTRY DATE: Entered STN: 10 Sep 1996
Last Updated on STN: 11 Oct 1996

AB Tertiary amine N-oxides of DNA intercalators with alkylamino sidechains are a new class of bioreductive drugs. N-oxidation masks the cationic charge of the amines, forming prodrugs with low DNA binding affinity and low toxicity which can be activated selectively by metabolic reduction under hypoxic conditions. This study compares three intercalator N-oxides (NC-NO, DACA-NO and AQ4N), which, respectively, give nitracrine (NC), DACA and AQ4 on reduction. In aerobic cell culture all three N-oxides were much less toxic than the corresponding amines, and showed large increases in cytotoxicity under hypoxia. The topoisomerase poisons DACA and AQ4 (and their N-oxides) were less active against non-cycling than cycling cells. However, only AQ4N was active against the mouse mammary turnout MDAH-MCa-4. This dialkylaminoanthraquinone-di-N-oxide has activity at least as great as the reference bioreductive drug RB 6145 against this turnout, both with and without radiation and when **combined** with the **tumour** blood flow inhibitor 5,6-**dimethylxanthenone** -4-acetic acid (**DMXAA**). It is suggested that the high in vivo activity of AQ4N relative to the other topoisomerase-targeted N-oxide, DACA-NO, may be in part due to release in hypoxic cells of an intracalator with sufficiently high DNA binding affinity that it is retained long enough to kill non-cycling cells when they eventually re-enter the cell cycle.

CC Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Nucleic acids, purines and pyrimidines 13014
Reproductive system - Pathology 16506
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Reproductive system and implantation studies 22028
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Tissue culture, apparatus, methods and media 32500

IT Major Concepts
Metabolism; Pharmacology; Reproductive System (Reproduction); **Tumor** Biology

IT Chemicals & Biochemicals
NITRACRINE N-OXIDE

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; DNA BINDING; MOUSE MAMMARY **TUMOR** ; N-(2-(DIMETHYLAMINO)ETHYL)ACRIDINE-4-CARBOXAMIDE N-OXIDE; NITRACRINE N-OXIDE; 1,4-BIS-((2-(DIMETHYLAMINO-N-OXIDE)ETHYL)AMINE)-5,8-DIHYDROXYANTHRACENE-9,10-DIONE

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

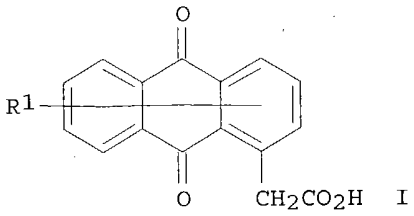
RN 20063-73-4 (NITRACRINE N-OXIDE)

L35 ANSWER 37 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:618127 HCAPLUS
DOCUMENT NUMBER: 123:17878
TITLE: Pharmaceutical compositions containing nitric oxide synthase inhibitors and anticancer agents
INVENTOR(S): Thomsen, Lindy Louise; Knowles, Richard Graham; Moncada, Salvador Enrique
PATENT ASSIGNEE(S): Wellcome Foundation Ltd., UK
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9509621	A1	19950413	WO 1994-GB2146	19941004 <--
W: AU, BR, CA, CN, CZ, FI, GE, HU, JP, KR, KZ, LT, NO, NZ, PL, RU, SI, SK, UA, US, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9477876	A1	19950501	AU 1994-77876	19941004 <--
ZA 9407754	A	19960404	ZA 1994-7754	19941004 <--
PRIORITY APPLN. INFO.:			GB 1993-20484	19931005 <--
			WO 1994-GB2146	19941004 <--

OTHER SOURCE(S): MARPAT 123:17878
GI



I

AB A pharmaceutical composition for treatment of cancer or reducing the tumor burden comprises a nitric oxide synthase inhibitor in **combination** with a cytokine-releasing anticancer agent. The anticancer agents are derivs. of 5,6-dimethylxanthenone acetic acid (DMX) I (R1 = alkyl, halogen, Ph, CF3, CN, NO2, NH2, CH2CO2H, OR2, SR2, SO2R2, NHR2, etc; R2 = alkyl, amino, methoxy). Tumor regressions induced by treatment with DMX (30 mg/kg i.p.) were not inhibited by the NO synthase inhibitor L-N-iminoethylornithine (L-NIO) (30 mg/kg s.c. followed by 100 mg/kg s.c. 8 h later) despite the fact that the dose used completely inhibited the increased NO generation. L-NIO increased systemic arterial pressure within 10 min of injection.

IC ICM A61K031-195
ICS A61K045-06
ICI A61K031-195, A61K031-12
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT **Neoplasm inhibitors**
(compns. containing nitric oxide synthase inhibitors and anticancer agents)
IT 36889-13-1 **117570-53-3 117570-53-3D**, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(compns. containing nitric oxide synthase inhibitors and anticancer agents)

L35 ANSWER 38 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1996:24828 BIOSIS
DOCUMENT NUMBER: PREV199698596963
TITLE: Hypoxia-activated prodrugs as **antitumour** agents: Strategies for maximizing **tumour** cell killing.
AUTHOR(S): Wilson, William R. [Reprint author]; Pruijn, Frederik B.
CORPORATE SOURCE: Sect. Oncol., Dep. Pathol., Univ. Auckland Sch. Med., Private Bag 92019, Auckland, New Zealand
SOURCE: Clinical and Experimental Pharmacology and Physiology, (1995) Vol. 22, No. 11, pp. 881-885.
ISSN: 0305-1870.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jan 1996
Last Updated on STN: 28 Feb 1996

AB 1. Hypoxia arises in solid **tumour** because of inefficient blood supply. While hypoxic cells are resistant to radiotherapy and probably to many chemotherapeutic drugs they can, in principle, be turned to advantage through the development of hypoxia-activated cytotoxic drugs (bioreductive drugs). 2. Three general approaches to exploiting **tumour** hypoxia are discussed. The first relies on fluctuating blood flow in **tumours** and the consequent cycling of cells through the hypoxic compartment. The second incorporates a prodrug approach in which drug activation gives rise to cytotoxic metabolites which diffuse out of hypoxic zones. The third utilizes selective inhibitors of **tumour** blood flow to induce additional hypoxia and thus enhance bioreductive drug activation. 3. The latter two approaches are illustrated by recent studies with the dinitrobenzamide nitrogen mustard class of bioreductive drugs and their **combination** with the **tumour** blood flow inhibitor 5,6-**dimethylxanthenone**-4-acetic acid.

CC Cytology - Animal 02506
Biochemistry - Gases 10012
Biochemistry studies - General 10060
Cardiovascular system - Physiology and biochemistry 14504
Blood - Blood and lymph studies 15002
Pharmacology - Cardiovascular system 22010
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cardiovascular System (Transport and Circulation); Cell Biology; Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
ACETIC ACID; NITROGEN MUSTARDS

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; BIOREDUCTIVE AGENTS; DINITROBENZAMIDE NITROGEN MUSTARDS; NSC 64394; **TUMOR** BLOOD FLOW INHIBITION; 5,6-**DIMETHYLXANTHENONE**-4-ACETIC ACID

RN 64-19-7 (ACETIC ACID)
55-86-7D (NITROGEN MUSTARDS)

L35 ANSWER 39 OF 42 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:297673 HCAPLUS
DOCUMENT NUMBER: 122:64319
TITLE: Cancer therapy, using antibody conjugates, in **combination** with a vasoactive agent

INVENTOR(S): Pedley, Rosamund Barbara; Begent, Richard Henry John
PATENT ASSIGNEE(S): Cancer Research Campaign Technology Ltd., UK
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2

DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9423753	A1	19941027	WO 1994-GB831	19940420 <--

W: JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: GB 1993-8166 A 19930420 <--
OTHER SOURCE(S): MARPAT 122:64319

AB The invention provides a two component system for the treatment of cancer comprising: (i) a tumor-directed antibody linked to a toxic agent or linked to an enzyme capable of converting a prodrug to a toxic agent; and (ii) an agent having the ability to restrict blood flow at the site of a tumor. Preferably the agent is a flavonoid derivative such as 5,6-dimethylxanthenone acetic acid or flavone acetic acid.

IC ICM A61K047-48
ICS A61K031-35
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1
IT **Neoplasm inhibitors**
(cancer therapy using antibody conjugates in **combination** with a vasoactive agent)
IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, cancer therapy using antibody conjugates in **combination** with a vasoactive agent)
IT Ricins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, with antibodies; cancer therapy using antibody conjugates in **combination** with a vasoactive agent)
IT 10043-66-0D, Iodine 131, conjugates with antibodies, biological studies 23214-92-8D, Adriamycin, conjugates with antibodies 87626-55-9D, conjugates with antibodies **117570-53-3D**, conjugates with antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cancer therapy using antibody conjugates in **combination** with a vasoactive agent)

L35 ANSWER 40 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1994:361430 BIOSIS
DOCUMENT NUMBER: PREV199497374430
TITLE: Enhancement of radioimmunotherapy by drugs modifying **tumour** blood flow in a colonic xenograft model.
AUTHOR(S): Pedley, R. Barbara [Reprint author]; Begent, Richard H. J.; Boden, Joan A.; Boxer, Geoffrey M.; Boden, Robert; Keep, Patricia A.

CORPORATE SOURCE: CRC Targeting Imaging Group, Dep. Clin. Oncol., Royal Free Hosp. Sch. Med., London NW3 2PF, UK
SOURCE: International Journal of Cancer, (1994) Vol. 57, No. 6, pp. 830-835.
CODEN: IJCNAW. ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 1994
Last Updated on STN: 12 Oct 1994

AB Radioimmunotherapy (RIT) is hampered clinically by poor **tumour** localization of antibody. In order to enhance localization we have investigated the concomitant use of RIT with 2 drugs, flavone-8-acetic acid (FAA) and its analogue 5,6-**dimethylxanthenone**-4-acetic acid (XAA), which both reduce **tumour** blood flow and induce immunomodulation. A single i.v. dose of 0.5 mCi (18.5 MBq) intact 131I anti-CEA antibody significantly delayed growth and prolonged survival over that of untreated controls, in an established LS174T colon xenograft model in nude mice. The adjuvant use of a single i.p. dose of either FAA or XAA, given 24 or 48 hr after 131I-A5B7 to allow maximum **tumour** levels of antibody to be attained before drug-induced blood-flow inhibition, significantly enhanced the RIT. FAA caused entrapment of antibody within the **tumour** in relation to the time allowed for localization before drug administration. Repeated doses of FAA prolonged **tumour** growth inhibition but did not enhance the therapy achieved after a single dose. Although both drugs alone induced massive **tumour** necrosis of all but a thin peripheral rim of viable cells, **tumour** regrowth was inhibited for a few days only, with no effect on survival. Drug-induced **tumour** necrosis, immunomodulation and retention of higher doses of 131I-A5B7 within the **tumour** may contribute to the enhanced RIT produced by this **combined** therapy.

CC Radiation biology - Radiation and isotope techniques 06504
Radiation biology - Radiation effects and protective measures 06506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Biochemistry studies - Minerals 10069
Anatomy and Histology - Regeneration and transplantation 11107
Movement 12100
Pathology - Therapy 12512
Digestive system - Pathology 14006
Cardiovascular system - Physiology and biochemistry 14504
Blood - Blood and lymph studies 15002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Cardiovascular system 22010
Pharmacology - Digestive system 22014
Pharmacology - Immunological processes and allergy 22018
Neoplasms - Immunology 24003
Neoplasms - Therapeutic agents and therapy 24008
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Cardiovascular System (Transport and Circulation); Clinical Endocrinology (Human Medicine, Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology; Physiology; Radiology (Medical Sciences)

IT Chemicals & Biochemicals
FLAVONE-8-ACETIC ACID; ACETIC ACID

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CARDIOVASCULAR-DRUG; FLAVONE-8-ACETIC ACID; IMMUNOLOGIC-DRUG; **TUMOR**; 5,6-**DIMETHYLXANTHENONE**

-4-ACETIC ACID
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 87626-55-9 (FLAVONE-8-ACETIC ACID)
64-19-7 (ACETIC ACID)

L35 ANSWER 41 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1994:317865 BIOSIS
DOCUMENT NUMBER: PREV199497330865
TITLE: **Combining** bioreductive drugs (SR 4233 or SN 23862) with the vasoactive agents flavone acetic acid or 5,6-**dimethylxanthenone** acetic acid.
AUTHOR(S): Cliffe, Stephen [Reprint author]; Taylor, Maryann L.; Rutland, Michael; Baguley, Bruce C.; Hill, Richard P.; Wilson, William R.
CORPORATE SOURCE: Section Oncol., Dep. Pathol., Univ. Auckalnd Sch. Med., Private Bag 92019, New Zealand
SOURCE: International Journal of Radiation Oncology Biology Physics, (1994) Vol. 29, No. 2, pp. 373-377. CODEN: IOBPD3. ISSN: 0360-3016.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 1994
Last Updated on STN: 1 Sep 1994

AB Purpose: To determine whether 5,6-**dimethylxanthenone** acetic acid (**DMXAA**), a potent analogue of flavone acetic acid (FAA) inhibits blood flow in mouse mammary **tumors**, and to assess whether **DMXAA** enhances the **antitumor** effects of Tirapazamine (SR 4233) and the novel bioreductive drug SN 23862 (a dinitrobenbenzene mustard). Methods and Material: MDAH-MCa-4 mouse mammary **tumors** were grown i.m. in the leg of C3H/HeN mice. **Tumor** blood flow was assessed by the pertechnetate clearance method and subsequent growth delay was determined in the same **tumors.** Results: Administration of **DMXAA** (65-70 mu-mol/kg) resulted in inhibition of **tumor** blood flow to approximately 25% of control values, with no recovery observed up to 36 h post-treatment. **Combination** of **DMXAA** with SR 4233 provided a significant increase in **tumor** growth inhibition relative to either drug alone. In this effect, **DMXAA** was qualitatively similar to FAA, but was approximately 10 times more potent. The interaction between **DMXAA** (65 mu-mol/kg) and SR 4233 (200 mu-mol/kg) was maximal with SR 4233 given between 15 min before and 60 min after **DMXAA.** For SN 23862, a similar enhanced growth delay was observed in **combination** with **DMXAA**, with no obvious time dependence between 15 min before and 4

h after **DMXAA.** When mean values for groups treated with SR 4233 (200 mu-mole/kg) alone and in **combination** with **DMXAA** (65-90 mu-mole/kg) were compared, a correlation was observed between **tumor** blood flow inhibition and subsequent growth delay. Conclusion: **DMXAA** is a potent inhibitor of blood flow in MDAH-MCa-4 **tumors. Combination** of this vasoactive drug with bioreductive agents leads to an enhanced **antitumor** effect. For SR 4233 and **DMXAA**, this enhanced effect may be predictable by measurement of **tumor** blood now inhibition shortly after drug administration.

CC Biochemistry studies - General 10060
Cardiovascular system - Blood vessel pathology 14508
Blood - Blood and lymph studies 15002
Reproductive system - Pathology 16506
Pharmacology - Cardiovascular system 22010
Pharmacology - Reproductive system and implantation studies 22028
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cardiovascular System (Transport and Circulation); Pharmacology; Reproductive System (Reproduction); **Tumor** Biology

IT Chemicals & Biochemicals
SR 4233; ACETIC ACID

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; MOUSE MAMMARY **TUMORS**; SN 23862; SR 4233; **TUMOR** BLOOD FLOW INHIBITION

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 27314-97-2 (SR 4233)
64-19-7 (ACETIC ACID)

L35 ANSWER 42 OF 42 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1995:80838 BIOSIS
DOCUMENT NUMBER: PREV199598095138
TITLE: Interaction between endotoxin and the **antitumour** agent 5,6-**dimethylxanthenone**-4-acetic acid in the induction of **tumour** necrosis factor and haemorrhagic necrosis of colon 38 **tumours.**
AUTHOR(S): Ching, Lai-Ming [Reprint author]; Joseph, Wayne R.; Zhuang, Li; Baguley, Bruce C.
CORPORATE SOURCE: Cancer Res. Lab., Auckland Univ. Sch. Med., Private Bag 92019, Auckland, New Zealand
SOURCE: Cancer Chemotherapy and Pharmacology, (1994) Vol. 35, No. 2, pp. 153-160.
CODEN: CCPHDZ. ISSN: 0344-5704.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Feb 1995
Last Updated on STN: 27 Apr 1995

AB The investigational **antitumour** agent 5,6-**dimethyl**-**xanthenone**-4-acetic acid (5,6-MeXAA) induced dose-dependent haemorrhagic necrosis of colon 38 turnouts to a similar extent to that

induced using bacterial lipopolysaccharide (LPS). TNF-alpha activity in serum and mRNA for TNF-alpha in splenocytes were induced over a broad range of LPS doses, whereas with 5,6-MeXAA, induction occurred only at concentrations approaching the maximum tolerated dose. At concentrations that provided similar degrees of haemorrhagic necrosis, the levels of serum TNF-alpha induced using 5,6-MeXAA were 100-fold lower than those obtained with LPS, indicating that haemorrhagic necrosis was not directly correlated with TNF-alpha levels. There was also no correlation between the degree of **tumour** necrosis and the duration of growth delay. Treatment with LPS did not induce a significant delay in growth, despite extensive **tumour** haemorrhagic necrosis, whereas with 5,6-MeXAA, treatments that improved the cure rate did not necessarily give longer growth delays. Therapy using a **combination** of sub-optimal doses of both compounds was synergistic for the induction of serum TNF-alpha and message for TNF-alpha but was not synergistic for **antitumour** efficacy. Thus, no correlation is evident between cure rates, duration of growth delay, haemorrhagic necrosis and TNF-alpha induction by 5,6-MeXAA or LPS.

CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Lipids 10066
Biochemistry studies - Carbohydrates 10068
Pathology - Necrosis 12510
Pathology - Therapy 12512
Metabolism - Carbohydrates 13004
Metabolism - Proteins, peptides and amino acids 13012
Digestive system - Pathology 14006
Cardiovascular system - Blood vessel pathology 14508
Endocrine - General 17002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Cardiovascular system 22010
Pharmacology - Digestive system 22014
Pharmacology - Immunological processes and allergy 22018
Toxicology - General and methods 22501
Neoplasms - Immunology 24003
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Physiology and biochemistry of bacteria 31000
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Cardiovascular System (Transport and Circulation); Digestive System (Ingestion and Assimilation); Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Pharmacology; **Tumor** Biology

IT Chemicals & Biochemicals
ACETIC ACID

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; LIPOPOLYSACCHARIDE; **TUMOR**; 5,6-**DIMETHYLXANTHENONE**-4-ACETIC ACID

ORGN Classifier
Enterobacteriaceae 06702
Super Taxa
Facultatively Anaerobic Gram-Negative Rods; Eubacteria; Bacteria; Microorganisms
Organism Name
Escherichia coli
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGN Classifier
Muridae 86375
Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 64-19-7 (ACETIC ACID)

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